21

Benign Prostate Hyperplasia and Chronic Kidney Disease

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1. Introduction

Benign Prostate Hyperplasia (BPH) is a common disease in adult men and its incidence is age related. On the basis of clinical criteria, the Baltimore Longitudinal Study of Aging found that the prevalence of BPH is approximately 25% in men aged 40 to 49 years, 50% in men aged 50 to 59 years, and 80% in men aged 70 to 79 years (Arrighi, Metter et al. 1991).

BHP is theoretically the detection of prostatic hyperplasia, which is the benign proliferation of the stroma and epithelium, by histological study. However histological studies for all men are unfeasible in clinical practice, so BHP usually refers to the palpable enlargement of the prostate, which can be detected by clinical or ultrasonographic examination, or presence of urinary symptoms loosely defined as lower urinary tract symptoms (LUTS), which are usually classified as obstructive or irritative (Levy and Samraj 2007).

Chronic kidney disease (CKD) encompasses a spectrum of different pathophysiologic processes associated with abnormal kidney function, and a progressive decline in glomerular filtration rate (GFR). *Chronic renal failure* (CRF) applies to the process of continuing significant irreversible reduction in nephron number, *end-stage renal disease* (ESRD) represents a stage of CKD where the accumulation of toxins, fluid, and electrolytes normally excreted by the kidneys results in the *uremic syndrome*. This syndrome leads to death unless the toxins are removed by renal replacement therapy, using dialysis or kidney transplantation (Fauci 2007). The prevalence of CRF using the Modification of Diet in Renal Disease equation is 26% in adults who are 70 years and older. Men are at 67% greater risk for advanced chronic renal failure and at 44% greater risk for end stage renal disease than women (Rule, Lieber et al. 2005).

Despite the many possible causes of obstructive uropathy, in studies of elderly patients with acute renal failure, the most common cause among all patients was BPH (Kumar, Hill et al. 1973; Tseng and Stoller 2009). Kumar et al., showed in their studies that acute renal failure in patients with obstructive uropathy were due to BPH (38%), neurogenic bladder (19%), obstructive pyelonephritis (15%).

Attending to high prevalence of BPH in older men with CKD it is invaluable to take into consideration the relationship between these two clinical entities. However, despite the high prevalence of CKD and BPH in elderly men, there is limited knowledge on the association between these two conditions.

The purpose of this chapter is to discuss the relationship between BPH and CKD, bearing in mind the epidemiology, pathophysiology, the clinical and imagiologic presentation of BPH and how it can contribute to CKD.

2. Epidemiology – Benign prostatic hyperplasia and chronic kidney disease

Benign prostatic hyperplasia is characterized by the nonmalignant overgrowth of prostatic tissue surrounding the urethra, ultimately constricting the urethral opening and giving rise to associated lower urinary tract symptoms (McVary 2006; Wei, Calhoun et al. 2008).

Diagnosis of BPH is made based on histologic examination of a prostatic tissue (biopsy, surgery or autopsy), however surrogate measures, namely lower urinary symptoms, bladder outlet obstruction and prostate enlargement are often used to define BPH as a clinical syndrome (Emberton, Andriole et al. 2003). For this reason, many consequences of BPH are not studied for it is impractical. This factgives us limited insight into the incidence and progression of the disease (Jacobsen, Girman et al. 2001). The prevalence of BPH thus can be calculated on the basis of histologic criteria (autopsy prevalence) or clinical criteria (clinical prevalence) (Wein 2007).

The 1984 milestone study by Berry and colleagues summarized the data from five studies demonstrating that no men younger than 30 had evidence of BPH and the prevalence rose with each age group, peaking at 88% in men in their 80s (Berry, Coffey et al. 1984).

BPH is considered a disease of aging male and can have a familial inheritance, especially if large prostate volumes and surgical intervention at a young age are seen in the pedigree (Wein 2007).

Definitions of BPH, have undergone several changes in the past decade, and, at present, no single criterion can be applied. In the past, the term "prostatism" was used, incorrectly referring to the prostate as the sole source of the typical LUTS (lower urinary tract symptoms) found in aging men. It has been pointed out that there are at least three interrelated phenomena that can be assessed independently, namely the symptoms (Wein 2007), enlargement of the prostate gland and presence of obstruction (Nielsen, Nordling et al. 1994). In a given patient, all three, two of the three, or only one of the three entities might be present. Paul Abrams was the investigator that changed the earlier and inappropriate term (prostatism) to lower urinary tract symptoms (LUTS) (Nielsen, Nordling et al. 1994; Abrams 1999)

BPH (histologically) is present in about 8% of men aged 31 to 40 years, and this prevalence increases markedly with age to about 90% by ninth decade(Berry, Coffey et al. 1984; Rosen, Altwein et al. 2003; McVary 2006). Studies in United States, England, Austria, Norway, Denmark, China, Japan, and India showed that the prevalence of BPH increases rapidly in the fourth decade of life, reaching nearly 100% in the ninth decade (Harbitz and Haugen 1972; Carter and Coffey 1990; Wein 2007) (Pradhan and Chandra 1975). It is striking that the age-specific autopsy prevalence is remarkably similar in all populations studied regardless of ethnic and geographic origin (Berry, Coffey et al. 1984).

However, we must take into account the aging population and increasing number of patients who need medical care for symptoms (LUTS) or consequences of BPH. Number of

consultations for BPH and urinary symptoms constitute the largest share of visits in our department and in urology departments worldwide. In 1989, there were approximately 1,3 million office visits to physician for BPH (Schappert 1993), and in 1992 approximately 170.000 prostatectomies were performed among inpatients in the United States (Xia, Roberts et al. 1999; Wei, Calhoun et al. 2008). Agency for Health Care Policy and Research Diagnostic and Treatment for BPH showed that from 22.5 million white men aged 50 to 79 years in the United States, in 1990, approximately 5.6 million needed medical consultation and treatment for BPH, demonstrating this disease is a prevalent health problem (Wei, Calhoun et al. 2008).

Although BPH is not a life-threatening condition, the impact of BPH on quality of life (QoL) can be significant and should not be underestimated (McVary 2006). According to the World Health Organization although the death rate attributable to BPH is negligible, the estimated DALY's (The sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability) due to BHP is quite considerable. Most of the disability is probably due to severe clinical symptoms and/or late complications of BPH like CKD (Organization 2011).

Chronic kidney disease is a serious condition associated with premature mortality, decreased quality of life, and increased health-care expenditures. Untreated CKD can result in end-stage renal disease requiring dialysis or kidney transplantation.

The 1999-2004 National Health and Nutrition Examination Survey (NHANES) determined that 16.8% of the U.S. population aged >20 years had CKD (according to 1999-2004 data), compared with 14.5% from the 1988-1994 NHANES, an increase of 15.9% based on crude estimates of prevalence (Saydah 2007) which reflects the increasing needs for health care policy for CKD.

3. The relationship between benign prostatic hyperplasia and chronic kidney disease – A consequence of urinary outflow obstruction?

Although the exact etiology of BPH is not known it seems (from recent studies and daily clinical practice) that the natural history and evolution of benign prostatic enlargement ends up in urinary obstruction causing degradation of renal function over time.

Both diseases are extremely common among aging male, leading some to suggest that it is a natural concomitant of aging (Wu, Li et al. 2006).

In his 1989 retrospective study of 19 patients who were admitted to renal dialysis units for end-stage renal disease caused by BPH, authors (Sacks, Aparicio et al. 1989) raised awareness of BPH as a cause for CKD and suggested a more adequate screening of renal function in men with untreated LUTS. More recently a cross-sectional survey in Spain of 2,000 randomly sampled men who were 50 years or older showed a 2.4% prevalence of self-reported renal failure related to a prostate condition (9% reported renal failure from any cause) (Hunter, Berra-Unamuno et al. 1996; Rule, Lieber et al. 2005). The main limitation of this study was that it relied on the self report of CKD, and no distinction between Acute Renal Failure (ARF) or CKD was made. Nonetheless it remains one largest studies that reveals a connection between CKD and BPH (Hunter, Berra-Unamuno et al. 1996). Another study (Hill, Philpott et al. 1993) showed that men presenting for prostate

surgery had a 7,7% prevalence of renal failure compared to a 3,7% prevalence in age matched men presenting for nonprostate surgery. This proves that renal failure in men with advanced BPH does not only reflect older age. Other statistical study revealed that men presented to urologist for BPH treatment showed an average of 13,6% of renal failure(McConnell, Barry et al. 1994).

The Rochester Epidemiology Project found a significant association between signs and symptoms of BPH and CKD in their population-based sample of 476 white men (Rule, Jacobson et al. 2005; Rule, Lieber et al. 2005). There was a significant association between CKD and moderate/ severe LUTS and peak flow rate of <15 mL/s. In conclusion there was a cross-sectional association between signs and symptoms of bladder outlet obstruction and chronic kidney disease in community-dwelling men (Rule, Lieber et al. 2005).

In contrast, a population-based study from Austria did not find LUTS to be an independent risk factor for impaired kidney function in men. A total of 2.469 men entered the cross-sectional study and 439 with CKD were assessed in longitudinal analysis. LUTS was assessed using the IPSS (International Prostate Symptom Score) questionnaire. There was no significant association between degree of LUTS and GFR after adjusting for age in this cross-sectional study (Ponholzer, Temml et al. 2006).

Furthermore a 30,466 men study from the HUNT II (Second Health Study in Nord-Trøndelag; 1995-1997) failed to show a connection between LUTS and CKD (Hallan, Kwong et al. 2010). Results have shown that men with moderate to severe LUTS, indicating BPH, did not have increased risk of future kidney failure after adjusting for age, and inclusion of men with such symptoms did not improve the effectiveness of a CKD screening strategy using kidney failure as the main outcome (Hallan, Kwong et al. 2010; Hallan and Orth 2010).

Nonetheless quite recently evidence of association between BPH and CKD has arisen in two different studies. In a recent study by Yamasaki *et* al, the Post-Void Residue (PVR) of the patients with CKD was significantly greater than that of the patients without CKD and the presence of post-void residual urine was independently associated with CKD, indicating a close association between CKD and residual urine. In this study the PVR is used as a surrogate measure of Bladder Outlet Obstruction (BOO) and thus of urodinamically relevant BPH (Yamasaki 2010). Authors reported a higher prevalence (31,8%) of CKD among BPH patients (Yamasaki 2010). In another study by Hong et al (Hong, Lee et al. 2010), the results showed that a decreased Qmax (Peak flow rate), with a history of hypertension and/or diabetes, were significantly associated with CKD in men seeking management for LUTS caused by BPH of various severity. Although the prevalence of CKD can be considered relatively low among men with BPH, the possibility of CKD should be considered in those who have a low Qmax, obstructive urinary symptoms, or have comorbidities such as hypertension and DM (Hong, Lee et al. 2010). In this study the authors report 494 patients from a group of 2741 BPH patients that were classified as having CKD (eGFR < 60 mL/min/1,73 m^2).

The 1994 Agency for Health Care Policy and Research created BPH clinical guidelines that recommended serum creatinine screening in men presenting with lower urinary tract symptoms, however a 2003 update discontinued the serum creatinine measurements (Rule, Lieber et al. 2005). These different approaches to BPH patients may lead to a significant amount of patients underdiagnosed for CKD.

As we take all this data into account, one should bear in mind that BPH is an almost ubiquitous condition in the old man. The low occurrence of CKD in BPH clinical trials should not be used to infer a weak association between the two disease processes. However it is clear that not all expressions of BPH are associated with CKD: Prostate volume, PSA (Prostate Specific Antigen) and even LUTS do not share a strong association with CKD (Rule, Jacobson et al. 2005; Ponholzer, Temml et al. 2006; Hallan, Kwong et al. 2010).

Bladder outlet obstruction signs and symptoms (QMax, PVR, Obstructive LUTS) are significant predictors of CKD (Rule, Jacobson et al. 2005; Yamasaki 2010), bladder outlet obstruction probably makes the bridge between CKD and BPH (Hong, Lee et al. 2010). This is probably a reflection of the etiology of CKD secondary to BPH.

We should also never forget that CKD is a multifactorial process, and it becomes difficult to separate the contribution of BHP from all the other renal insults. This also takes its toll on the design of the studies as many men with concomitant disease are excluded, and thus making it harder for investigators to take into account the true influence of BPH on CKD.

4. BPH physiopathology, disease progression and renal failure

The exact etiology of BPH is unknown, however the similarity between BPH and the embryonic morphogenesis of the prostate has led to hypothesis that BPH may result from a reawakening of embryonic induction process in adulthood (Oesterling 1996; McVary 2006).

The most common renal pathology finding in men with obstructive nephropathy due to BPH is chronic interstitial nephritis (Coroneos, Assouad et al. 1997; Rule, Lieber et al. 2005) and 30% of cases have been attributed to obstructive uropathy.

Late or end stage renal failure secondary to prostatic or bladder outflow obstruction should be amenable to prevention if cases are recognised early, however it still difficult to recognise which men with BPH are at risk of renal failure and need close investigation. For this reason we truly believe that is important to recognize factors that can be measured and are important bases or risk factors for the evaluation and treatment of BPH.

To assess BPH as risk factor for chronic kidney disease or renal failure it is important to understand the surrogate measures often used to diagnose BPH. These factors are essentially clinical, anatomical and physiological.

4.1 Benign prostate enlargement

BPH/BPE first develops in the periurethral *transition zone* of the prostate. The transition zone consists of two separate glands immediately external to the preprostatic sphincter. Prostate enlargement also involves an increase in the number of glands, particularly the periuretheral glands, and increase in smooth muscle and connective tissue in the periuretheral region of the prostate (McNeal 1978; Rule, Lieber et al. 2005; Wein 2007). Prostate size can be estimated by digital rectal examination (DRE) (underestimate true prostate size) but reliability across observers is in general considered poor (Wein 2007), for these reasons in all cross-sectional studies prostate volume is assessed by TRUS (trans-rectal ultrasound).

In the physiological point of view, as the prostate enlarges, it compresses the urethra, preventing the outflow of urine and contributing to the common lower urinary tract symptoms.

Previous studies which examined the association between prostate size and renal function gave conflicting results (Rule, Lieber et al. 2005), some showing a strict relation between prostate size and GFR (Olbrich, Woodford-Williams et al. 1957) but other studies did not (Terris, Afzal et al. 1998)

Other authors, like Shapiro *et* al. emphasize the role of prostatic smooth muscle in pathophysiology of BPH (Shapiro, Hartanto et al. 1992). These authors advocated that the amount of muscle in prostate size and its contractile properties are an important factor in BPH. Smooth muscle cells in are not optimal for force generation. They present a downregulation of smooth muscle myosin heavy chain and a significant upregulation of nonmuscle myosin heavy chain, suggesting either proliferation or loss of normal modulation pathways (Lin, Robertson et al. 2000). Factors that determine passive tone in prostate remain to be elucidated (Wein 2007). However it is known that active muscle tone in human prostate is regulated by adrenergic nervous system (Schwinn 1994). Adrenergic neurotransmitters have been involved in prostate smooth muscle regulation as well as contraction, and α-adrenergic blockade leads to a significant downregulation of normal protein gene expression, specifically smooth muscle myosin heavy chain (Boesch, Dobler et al. 2000; Wein 2007).

Recent studies were made to relate prostate size and LUTS in BPH. Hassanzadeh *et.* al, found a significant correlation between urgency and prostate size (Hassanzadeh, Yavari-kia et al. 2010), which can be considered as predictive factor for the disease and probably a strong link between BPE and CKD.

So, prostate and its enlargement can contribute for outflow obstruction not only by is static component (periurehral compression caused by stromal component) but also dynamic component (smooth muscle cells and adrenergic pathway). Prostate growth is only one of the components of LUTS in aging men.

4.2 Lower Urinary Tract Symptoms (LUTS)

Lower urinary tract symptoms (LUTS) are clinical criteria to define a man with urinary problems. Most of the men with BPH have voiding dysfunction, complaining with nocturia, urgency, week urinary stream, increased urinary frequency and sense of incomplete bladder emptying after micturition.

Many studies were done to achieve a scientific relation between LUTS and CKD, however until recent years there was no palpable evidence connecting these two entities. Hill et al. in a retrospective study did not find any relation between duration of symptoms and serum creatinine levels (Hill, Philpott et al. 1993). Likewise Gerber *et* al. did not achieve any success in linking serum creatinine levels and LUTS (Gerber, Goldfischer et al. 1997). Hong *et* al., reported that although there was no significant association between overall symptoms (IPSS score) with CKD, individual obstructive symptoms such as hesitancy and/or weak stream was significantly associated with CKD status (Hong, Lee et al. 2010)

Our clinical practice shows us that many men with LUTS do not value their symptoms, and do not seek medical care. Those older men often tolerate and disregard their lower urinary

tract symptoms. In our opinion under reported symptoms can induce a significant bias in most of studies already done.

Although many patients who do not value their symptoms, mainly the older ones, the frequency of symptoms and its interference with quality of live (QoL) is the principal factor that drive men to consult a physician (Hong, Rayford et al. 2005).

Patient perceptions are receiving greater emphasis as part of clinical decision-making (Jacobsen, Guess et al. 1993; Roberts, Rhodes et al. 1994). The variability of relationships between symptom severity and the likelihood that the symptoms relate with CKD requires further investigations. However one must take into account that the absence of lower urinary tract symptoms in older man does not necessarily exclude BPH with urinary outlet obstruction. Moreover, whether symptoms can be graded according to severity (International Prostate Symtpoms Score – IPSS) this does not predict the degree of obstruction to urinary flow. However, when men with complete chronic urinary retention and severe symptoms needing surgical intervention were evaluated, the authors found as much as 30% of men with renal insufficiency (Sacks, Aparicio et al. 1989).

4.3 Post-voiding residual urine volume – Chronic urinary retention

Chronic urinary retention is thought to be the dominant mechanism by which BPH can cause chronic renal failure (Rule, Lieber et al. 2005). Rule *et* al, defined chronic urinary retention (CUR) as a post-void residual urine (PVR) higher than 100 mL, and reported that CUR was significantly associated in CKD in community-dwelling men. For years it has been well described that large volumes (»300 mL) affect renal function in advanced BPH (Styles, Neal et al. 1988; Rule, Lieber et al. 2005; Yamasaki 2010).

Recent studies, however, demonstrate that the volume of residual urine (post void) necessary to impair renal function is not that elevated. Yamasaki et al, verified in their study a cut-off of 12 ml for PVR (Yamasaki 2010), confirming PVR as a significant and independent risk factor for CKD. This study showed for the first time that patients with BPH can develop impaired renal function with small amounts of post-void urine (PVR< 100 ml). Furthermore, these findings indicated a higher prevalence of CKD in patients with BPH, acknowledging it as a risk factor for CKD. However, the mechanism by which small PVR influence renal function remains unknown.

Although, as Yamasaki et al. demonstrated low post-void residual urine can cause deterioration of renal function it is scientifically accepted that large residual pos-void urine are in line more severe cases of renal function deterioration (Yamasaki 2010).

4.3.1 Acute urinary retention

Acute urinary retention (AUR) is defined as an acute complication of benign prostatic hyperplasia, patients suffers from an acute, sudden and painful inability to micturate. AUR represents an immediate indication for intervention or even surgery. Between 25% and 30% of men who underwent transurethral resection of prostate (TURP) had AUR as their main indication (Wein 2007). This complication is not exclusive for patients suffering from BPH, other causes can trigger acute urinary retention, like surgery, anaesthesia, trauma, medications, medical examination and urinary tract infections (mainly prostatitis).

In 2002 the self-reported rate of AUR in a cross sectional study in Spanish men was 5.1% (Hunter, Berra-Unamuno et al. 1996).

Acute urinary retention is not common in men under sixty years, and may be responsible for the majority of acute renal failure cases due to obstructive uropathy (Prakash, Saxena et al. 2001). Men in whom acute urinary retention is promptly relieved by bladder catheterization acute renal failure does not develop but long-term tubular dysfunction may still occur (Rule, Lieber et al. 2005). It is believed that acute urinary retention without prior history of chronic urinary retention do not lead to chronic renal failure. High bladder compliance allows men to maintain a normal GFR, however renal tubular dysfunction may persist after the acute urinary retention episode and probably result in progressive renal disease.

4.4 Bladder remodelling – Bladder response to urinary obstruction

The bladder has a central role in pathophysiology of BPH and its complications.

Current evidence suggests that the bladder´s response to obstruction is largely an adaptative one, although it is only a partially adptative one. It is also clear for many authors and physicians that LUTS in men with BPH or prostate enlargement are more closely related to obstruction-induced changes in bladder function than to the outflow obstruction directly.

There are of two types of bladder changes. First, changes that lead to detrusor instability (clinically associated with symptoms of frequency and urgency). Second, changes associated with decreased detrusor contractility (emptying symptoms – low urinary stream, hesitancy, intermittency, increased residual urine) and detrusor failure (Wein 2007).

The development of bladder wall thickening (easily measurable by ultrasound) and trabeculation due to smooth muscle hypertrophy and connective tissue permeation is responsible for increased bladder pressure in patients with high pressure chronic retention (Jones, Ellis et al. 1991; Rule, Lieber et al. 2005). Gosling *et* al, were some of the first authors who established endoscopically that major detrusor changes and trabeculation were due to an increase in detrusor collagen (Gosling and Dixon 1980). Severe trabeculation is related to significant residual urine, suggesting that increased collagen in the bladder wall is probably responsible for incomplete bladder emptying to rather than impaired muscle function (Wein 2007). Detrusor hypertrophy is one of the first modifications in the bladder and, as in animal models, the initial response is the development of smooth muscle hypertrophy (Gosling, Kung et al. 2000; Levin, Haugaard et al. 2000). This is an adaptative response associated with intra and extracellular changes in the smooth muscle cells that leads to detrusor instability. Obstruction also induces changes in smooth muscle cells contractile protein expression, impairing cell-to-cell communication (Levin, Haugaard et al. 2000), with changes in myosin heavy chain isoform expression (Lin, Robertson et al. 2000) that lead to detrusor instability and in some cases to impaired contractility (Wein 2007).

Cellular and physiological changes in bladder muscle and collagen, contribute to a high pressure bladder that perpetuates itself with worsening ability to empty and causing kidney lesions.

These mechanisms of bladder remodelling develop in a hypofunctional bladder, with low compliance. Comiter *et* al. reported that in a series of men with symptomatic BPH, 78% of

patients with low bladder compliance had renal failure (Comiter, Sullivan et al. 1997). Low bladder compliance and detrusor instability may be causal mechanisms for renal failure in men in chronic urinary retention (Rule, Lieber et al. 2005).

In other studies (animal experimental studies) in addition to obstruction-induced changes in the smooth muscle cell and collagen of the bladder wall, there was clear evidence that obstruction may modulate neural-detrusor responses, causing reduced bladder contractility and altered sensation (Chai, Andersson et al. 2000)

Bladder remodelling is a response to continued bladder obstruction, and detrusor smooth muscle cell is a key contributor to the complex symptoms associated with prostatic obstruction (Christ and Liebert 2005), namely in BPH/BPE (benign prostatic enlargement).

4.5 Ureterovesical junction and upper tract dilation

In general, ureterovesical junction obstruction caused by bladder remodelling in chronic urinary retention is a contributing mechanism for renal failure in BPH (Rule, Lieber et al. 2005). Upper tract dilation occurs as a consequence of a continuum bladder outlet obstruction and remodelling (detrusor hypertrophy and scarring) leading to anatomical ureterovesical junction obstruction (Jones, Ellis et al. 1991). Upper urinary tract dilation or hydronephrosis is consistent with chronic renal failure from obstructive uropathy. In men with BPH and increased serum creatinine, hydronephrosis is common (one third), and is found in 90% of men with BPH who are hospitalized for uremic symptoms (Sacks, Aparicio et al. 1989). In ultrasound evaluation it is common among patients with bilateral hydroureteronephrosis to observe compressing and thinning of renal cortex, with obvious impact in renal function. A history of enuresis, painless chronic retention, and palpable bladder should suggest a diagnosis of high pressure chronic retention with its attendant risk of hydroureteronephrosis (Sacks, Aparicio et al. 1989).

4.6 Other causes

Recurrent urinary tract infections in men with chronic urinary retention due to BPH may also contribute to chronic renal failure (Rule, Lieber et al. 2005).

Secondary hypertension due to chronic urinary retention is also a described complication of BPH, leading to hypertensive kidney disease (Ghose and Harindra 1989).

Nephrogenic diabetes insipidus caused by partial or chronic urinary obstruction can result in renal failure (Klahr 2001).

Other clinical entities like diabetes and hypertension are independent factors that can lead to CKD (Gerber, Goldfischer et al. 1997). Patients with BPH are probable carriers of these pathologies that are likely to seriously aggravate renal function and must be taken into account as sombre conditioners of renal disease.

5. Clinical presentation

BPH is a chronic and progressive condition (Jacobsen, Girman et al. 2001) patients generally have a history of lower urinary tract symptoms and indolent obstructive uropathy.

Clinical presentation of BPH/obstructive uropathy varies and reflects the source and duration of obstruction. In BPH, symptoms results from the direct bladder outlet obstruction (BOO) from enlarged tissue (static component) and the increased smooth muscle tone and resistance within the enlarged gland (dynamic component). This physiologic issues reflect in voiding dysfunctions, that significantly affects the health and quality of life of many older men.

Most of the patients have characteristic symptoms. Patients' complaints are usually nocturia, urgency (imperious will to hold urine, some with complaints of incontinence), weak urinary stream (with decreased flow rate, low values in Qmax and Qaverage), a sense of incomplete bladder emptying, straining during micturition, increased micturition frequency and dribbling during or after urination (Rule, Lieber et al. 2005). Physical examination consists in a digital rectal examination (evaluating prostate characteristics and volume) and lower abdominal percussion and palpation to assess for bladder distension.

Recurrent or persistent urinary tract infections (UTI) are associated with prolonged urinary stasis of lower urinary tract obstruction, dysuria, frequency, urgency and hematuria are common complaints among men with UTI.

Chronic urinary retention as consequence of BPH has been defined as a palpable bladder that corresponds to a high PVR (Neal 1990), and most of the patients with chronic urinary retention have an indolent and progressive disease, with worsening of urinary symptoms and the majority of these patients just seek for medical care in bad health conditions with sharp renal insufficiency. It is always necessary to investigate symptoms and signs of chronic renal failure – nausea, vomiting, lethargy, edema and hypertension, that occur at late stage, usually with irreversible renal damage (Sacks, Aparicio et al. 1989), principally in older patients with other comorbidities (mainly diabetes and hypertension). In rare cases patients who resort to the emergency room because of anuria, require interventional procedures like indwelling catheter, nephrostomy (uni or bilateral) and sometimes (depending the level of renal function) hemodialysis.

Although signs and symptoms of BPH are normally present, there are a significant number of patients that are relatively asymptomatic (Tseng and Stoller 2009) (without significant voiding dysfunction), but can present primarily clinical sequel of renal insufficiency – uremia; with nausea, vomiting and mental status changes – and analytical changes – electrolyte disturbances (hypercaliemia and nonanion gap acidosis).

Older patients with voiding dysfunctions caused by chronic urinary obstruction, might present hypertension due to hypervolemia in the case of bilateral obstruction or increased renin release (Tseng and Stoller 2009). Hypertension, on other hand can be itself the sole cause of renal failure.

The development and validation (for different languages) of the standardized, self-administered symptom index (International Prostate Symptom Score [IPSS]) has been a critical event in the clinical research on LUTS and BPH (Cockett, Barry et al. 1992; Wein 2007). This diagnostic and follow-up tool is extraordinary, and the availability of validated translations in many common languages allows cross-cultural comparisons among man with BPH or LUTS from other causes.

In addition the enumeration of symptoms by frequency and time of occurrence, the bother associated with the symptoms, interference with activities of daily living, and the impact the

symptoms have on quality of life are important in distinguishing characteristics that we must take into account in evaluation of BPH patients. (Wein 2007).

Left untreated, BPH can cause serious complications including renal failure can occur, as acute renal failure (discussed above), urinary tract infections, bladder stones, hematuria, incontinence and mortality related with BPH.

5.1 Other complications of benign prostatic hyperplasia

5.1.1 Mortality

La Vecchia et al, reported that in the early 1980s, overall mortality from BPH ranged between 0,5 and 1,5/100 000 in most western European countries (La Vecchia, Levi et al. 1995). Between the early 1950s and the late 1990s, the overall mortality from BPH in the European Union (EU) fell from 5.9 to 3.5 per million, and the decline since the late 1950s was over 96%. Comparable falls were observed in the USA and Japan, and BPH mortality rates in the late 1990s were lower than in the EU (1.8/10(6) in the USA, 1.4 in Japan). BPH mortality trends were downwards also in the Eastern Europe, although rates in the late 1990s were about fourfold higher than in the EU (Levi, Lucchini et al. 2003).

Recent works have proven decreasing mortality rates related with BPH. The fall in BPH mortality, evident in statistics on underlying cause, was confirmed by statistics on all certified causes of death. In England, underlying-cause mortality reduced from 9.2 deaths per million in 1995 to 4.5 deaths per million in 2006 (Duncan and Goldacre 2011). The fall is remarkable in scale, likely to be attributable to clinical care, and could be regarded as an indicator of improving standards of care (Duncan and Goldacre 2011).

It is important to remember that patients in renal failure have an increased risk for complications following TURP compared with patients with normal renal function (25% versus 17%) (Holtgrewe, Mebust et al. 1989) and the mortality increases up to sixfold (Holtgrewe and Valk 1962; Melchior, Valk et al. 1974).

5.1.2 Bladder stones

In a large autopsy study the prevalence of bladder stones was eight times higher in men with a histological diagnosis of BPH (3.4%) than in control subjects (0.4%), but no increased incidence of ureteral or kidney stones was found (Grosse 1990). Bladder stones are in line with urinary retention, stasis and urinary infection, factors that propitiate ion aggregation and stone nucleation.

5.1.3 Urinary tract infections

In previous surgical series, urinary tract infections (UTIs) constitute the main indication for surgical intervention (12% of patients) (Holtgrewe, Mebust et al. 1989). Urinary tract infections are generally due to chronic urinary obstruction caused by increased amounts of residual urine, that predispose to UTIs (Mebust, Holtgrewe et al. 1989).

5.1.4 Urinary incontinence

Incontinence is one of the most feared complications from surgical intervention for BPH (McConnell, Barry et al. 1994), although it may be the result of BPH secondary to

overdistention of the bladder (overflow incontinence) or to detrusor instability. It is estimated to affect up to one half or more of all obstructed patients (urge incontinence) (McConnell, Barry et al. 1994; McConnell, Bruskewitz et al. 1998; Wein 2007).

5.1.5 Hematuria

Gross hematuria with clots with no other identifiable cause is common among BPH patients. Faubert *et* al, showed more than 30% of patients with microscopic or gross hematuria (Faubert 1998). Evidence suggests that in the patients predisposed to hematuria the micro-vessel density in prostate is higher than in controls (Wein 2007), suggesting that vascular lesions can be the cause of hematuria.

6. Diagnostic tests

Although nowadays it is increasingly rare to find a patient with chronic renal failure from chronic urinary retention due to BPH, about 13,6% (range from 0,3 to 30%) of men with BPH may present with CKD defined by a baseline serum creatinine of more than 133 mmol/L (1,5 mg/dL). This is particularly true in older patients with cognitive deterioration and autonomy impairment. In order to diagnose and monitor the impact of a bladder outlet obstruction due to BPH in the upper urinary tract, some laboratory and imaging tests should be considered: standardized questionnaires, serum creatinine levels or estimated glomerular filtration rate (eGFR), urinalysis, serum prostatic specific antigen (PSA) levels, uroflowmetry with peak flow rate determination, renal ultrasonography, bladder ultrasonography with detrusor thickness evaluation, transrectal prostate ultrasonography, pre and post-void residual urinary volume, cystometry, other urodynamic studies and urethrocystoscopy.

6.1 Symptom assessment by standardized questionnaires

BPH Impact Index (BII) is a questionnaire that assesses the effect of symptoms on everyday life and their interference with daily activities, and thus aimes to capture the impact of the condition. This questionnaire can be administered in conjunction with the IPSS and provides useful additional information (AUA 2010).

Symptom quantification is useful for diagnosis, determination of disease severity and monitoring of BPH. IPSS has become the international standard. It is derived from the American Urological Association Symptom Index (AUA-7 or AUA SI) described by Barry and colleagues in 1992 (Barry, Fowler et al. 1992; Barry, Fowler et al. 1992).

A recent multivariate analysis conducted by Hong *et* al., found associations of individual symptoms from the IPSS questionnaire and CKD status – obstruction-related symptoms, e.g. weak stream and hesitancy were significantly associated with CKD in age and comorbidity-adjusted analyses (Hong, Oh et al. 2010). Irritative symptoms, on the other hand, had no positive correlation with CKD. According to a subsample from the Olmsted County Study, moderate to severe LUTS (IPSS > 7) were positively correlated with CKD (Rule, Lieber et al. 2005). Kidney failure risks were 2.60 (CI 95%, 1.47-4.58) and 4.08 (CI 95%, 1.74-9.53) times higher for men with moderate and severe LUTS compared with men with no or mild LUTS, respectively ($p<0,001$) (Hallan, Kwong et al. 2010). However, after adjusting for age and

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5
Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
Urgency Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5
Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
	None	1 time	2 times	3 times	4 times	5 times or more
Nocturia Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5
Total IPSS Score						

Table 1. International Prostate Symptom Score (IPSS).

Additional Question:

	Delighted	Pleased	Mostly satisfied	About equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
Quality of life due to urinary symptoms If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Table 2. Additional Question evaluating quality of life.

Total score:
0-7 Mildly symptomatic
8-19 Moderately symptomatic
20-35 Severely symptomatic

therefore in isolation, IPSS is not a basis for kidney failure screening (Hallan, Kwong et al. 2010). Kidney function decreases with age and age significantly correlates with LUTS. Ponholzer A. *et* al also concluded that LUTS was not associated with increased loss of kidney function (Ponholzer, Temml et al. 2006).

Even though symptom score assessment do not directly correlates with CKD or can't be used to establish the diagnosis of BPH, it may serve as a basis for symptom severity and management approach to patients with LUTS. Further testing should be considered in patients with an IPSS score ≥ 8.

6.2 Serum creatinine

For decades, medical textbooks have stated that patients with BPH should have serum creatinine measured (Humes 2000; Goldman 2008). Clinical practice guidelines disagree on serum creatinine screening among men being evaluated for LUTS. The routine measurement of serum creatinine levels is not indicated in the initial evaluation according to the AUA Guideline Management of BPH (AUA 2010). This recommendation is based on the conclusion that baseline renal insufficiency appears to be no more common in men with BPH than in men of the same age group in the general population. On the other hand, the EAU Guidelines on BPH (2004) and the nephrology-focused NICE (National Institute for Health and Clinical Excellence) guidelines for the United Kingdom advocate that it is probably cost effective to measure serum creatinine levels in all patients. This is based on the fact that bladder outlet obstruction due to BPH might cause hydronephrosis and renal failure (Sacks, Aparicio et al. 1989).

Patients with BPH and renal insufficiency have much higher postoperative complications (25% complication rate compared with 17% for patients without the condition) and mortality (up to

sixfold) than those with normal renal function (Holtgrewe and Valk 1962; Melchior, Valk et al. 1974; Mebust, Holtgrewe et al. 2002). Most studies have found that the incidence of azotaemia in men with BPH varies from 15-30% (Mukamel, Nissenkorn et al. 1979). The Agency for Health Care Policy and Research (AHCPR) and the Fourth International Consultation on BPH highly recommends serum creatinine evaluation (McConnell, Barry et al. 1994). MTOPS data suggest that creatinine measurement is not necessary if voiding is normal. Estimated glomerular filtration rate (eGFR) is a more reliable measure to define CKD and is preferred over simple creatinine measurement (Roehrborn 2008).

6.3 Urinalysis

Urinalysis is a simple and inexpensive test that is recommended for the primary evaluation of a patient with suspected BPH. It is used to rule out urinary tract infection and hematuria. On the other hand, the finding of proteinuria/microalbuminuria may be indicative of renal failure.

6.4 Total PSA

Total PSA should be offered to patients with more than 10 years of life expectancy and in whom the PSA measurement may change the management of the symptoms (AUA 2010). In conjunction with digital rectal examination (DRE), total PSA measurement is the cornerstone of prostatic basic screening. PSA and prostatic volume can be used to evaluate the risks of either needing surgery or developing acute urinary retention.

6.5 Uroflowmetry / Peak urinary flow rate

Uroflowmetry is a simple and noninvasive urodynamic test that allows an objective evaluation of the patient micturition. Even though uroflowmetry is an unspecific evaluation, the micturition graphic may show some recognizable patterns (e.g. meatal stenosis, urethral stricture, BPH) and represent a reproducible way to quantify the strength of the urinary stream. It is a useful preoperative test. Peak urinary flow rate (PFR), or Qmax, appears to predict surgical outcome – patients with a preoperative Qmax > 15 mL/s have poorer outcomes than patients with preoperative Qmax < 15 mL/s do. PFR is an independent predictor for CKD rather than reported LUTS by standardized questionnaires (Hong, Lee et al. 2010). A study conducted by Rule *et* al. in community-dwelling men showed that men with CKD were more likely to have a slow urinary stream (Qmax < 15 mL/s) considering CKD as serum creatinine > 133 µmol/L or as eGFR < 60 mL/min/1,73 m^2. (Rule, Jacobson et al. 2005).

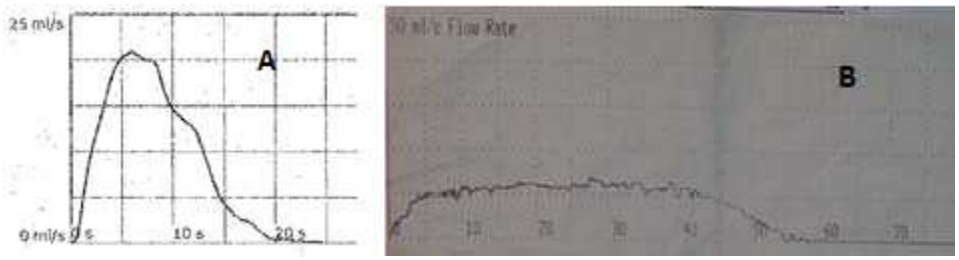

Fig. 1. Uroflowmetry. A) Normal patient; B) BPH patient.

6.6 Renal ultrasonography

Koch *et* al., performed renal ultrasound scans in a consecutive series of 556 elderly men with LUTS. 14 (2.5%) had hydronephrosis and serum creatinine levels appeared to be correlated with dilatation of the renal pelvis. The authors concluded that renal ultrasound is only indicated in patients with an elevated serum creatinine level and/or post-void residual urine volume (Koch, Ezz el Din et al. 1996). Renal ultrasonography has many advantages over intravenous urography (IVU) for upper urinary tract imaging: simultaneous evaluation of the bladder, post-void residual urine volume and prostate, better characterization of eventual renal masses, no radiation, no side-effects and lower cost.

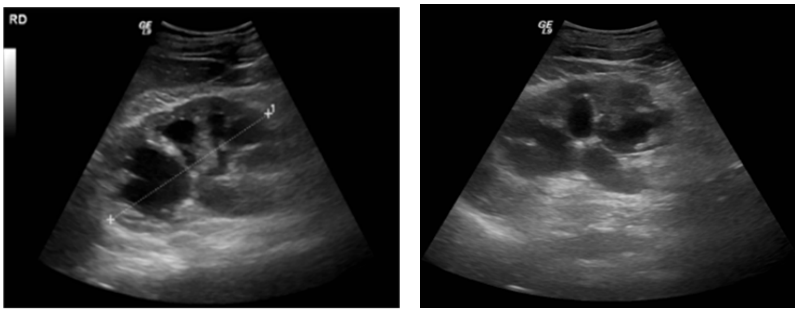

Fig. 2. Renal Ultrassound. Two ultrasound scans in BPH patient showing bilateral (right and left kidney respectively) ureterohydronephrosis.

6.7 Bladder ultrasonography

Chronic urinary retention leads to bladder wall thickening with trabeculations via smooth muscle hypertrophy and connective tissue infiltrates (Jones, Gilpin et al. 1991). This can lead in to a decline in bladder compliance with consequent functional or mechanical obstruction at the ureterovesical junction (Sutaria and Staskin 2000). More recently, the measurement of bladder wall thickness by transabdominal ultrasound has gained considerable interest as a non-invasive tool to assess bladder outflow obstruction (Kojima, Inui et al. 1997). Ultrasonic measurement of detrusor wall thickness at the anterior wall of bladders filled with ≥ 250 mL can securely detect bladder outlet obstruction if the value is ≥ 2 mm (Gabuev and Oelke 2011).

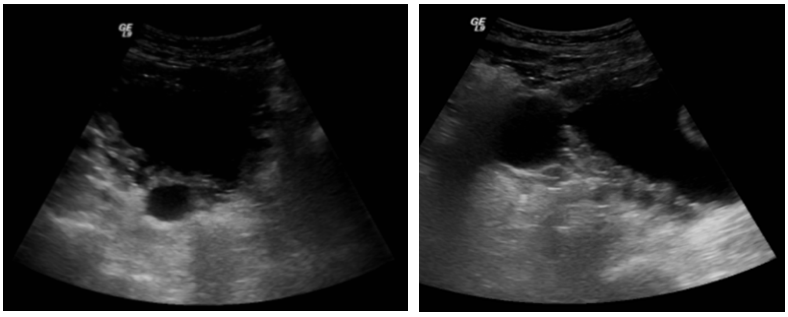

Fig. 3. Bladder Ultrassound. Two ultrasound scans in BPH patient. It is possible to observe the trabecullation, bladder wall thickening and diverticulum.

Manieri *et* al. concluded that bladder wall thickness appeared to be a useful predictor of bladder outlet obstruction, with a value exceeding that of uroflowmetry (Manieri, Carter et al. 1998). However, measurement of bladder wall thickness is currently not part of the recommended diagnostic work-up of patients with LUTS because reliable data on inter- and intra-observer variability, as well as reproducibility, are still lacking.

6.8 Post-void residual urine evaluation

Post-void residual urine volume can be measured with sufficient accuracy noninvasively by transabdominal ultrasonography. The measurement variation caused by the method is less than the biologic range of PVR variation (McConnell, Barry et al. 1994). It may also be measured by invasive methods (catheterization).

It has been well described that large residual urine volumes (>300 mL) affect renal function in advanced BPH (Neal, Styles et al. 1987; Rule, Jacobson et al. 2005). A PVR of more than 100 mL is defined as chronic urinary retention which is significantly associated with CKD in community-dwelling men (Rule, Jacobson et al. 2005). Nevertheless, small residual urine volumes (<100 mL) may also affect renal function as the presence of PVR relates with renal function regardless of the quantity of PVR (Yamasaki, Naganuma et al. 2011). Thus ultrasonographic evaluation of post-void residual is a useful test in the prevention of CKD secondary to BPH. Chronic urinary retention is related with CKD (Rule, Jacobson et al. 2005).

6.9 Prostate TRUS

Prostate transrectal ultrasonography (TRUS) is performed to assess prostate size and shape, tissue characterization and occult carcinoma. There is no relationship between prostatic enlargement measures and CKD (Rule, Jacobson et al. 2005).

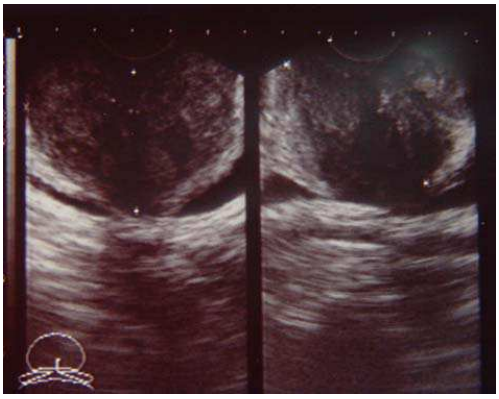

Fig. 4. Prostate Ultrassound. Prostate transrectal ultrasonography (sagital view).

6.10 Cystometry

It is not a routine exam for BPH evaluation. However, cystometry can help to identify high bladder pressure, low bladder compliance and detrusor instability that considerably affects renal function (Rule, Lieber et al. 2005; Yamasaki, Naganuma et al. 2011).

6.11 Pressure-flow studies

Pressure-flow studies can differentiate between patients with a low Qmax secondary to obstruction and those whose low Qmax is caused by a decompensated or neurogenic bladder. They are most useful for distinguishing between bladder outlet obstruction and impaired detrusor contractility.

6.12 Urethrocystoscopy

Urethrocystoscopy should not be done routinely but is optional during later evaluation if invasive treatment is strongly considered (McConnell, Barry et al. 1994). Nevertheless, it is a useful preoperative procedure to plan the most appropriate approach. This investigation can confirm causes of outflow obstruction while eliminating intravesical abnormalities.

7. Treatment

Patients with mild symptoms are most appropriately managed by watchful waiting, patients with moderate symptoms should receive pharmacotherapy and patients with severe bother most benefit from surgical management. A man with preoperative IPSS ≥ 17 has an 87% chance of experiencing a substantial symptom reduction (Meigs, Mohr et al. 2001).

A group of patients at increased risk of progression can be identified on the basis of specific risk factors (e.g. age, symptoms, PSA level, Qmax, prostate volume and post-void residual urine). It might be appropriate to identify these patients at risk of progression and initiate early preventative treatment (Emberton et al., 2003)(Gabuev and Oelke 2011). For example, a higher frequency of kidney failure in patients presenting for prostate surgery than for nonprostate surgery has been shown, and several studies have shown improvement in kidney function after prostatectomy (Hill et al., 1993).

7.1 Acute treatment

Patients who present to the emergency department with bladder outlet obstruction and high serum creatinine should receive a urethral catheter and subsequently evaluated in order to distinguish between acute and chronic renal failure. Hospitalization is often required in these cases. If ureterohydronephrosis and azotaemia persists despite bladder desobstruction, an ureterovesical junction obstruction should be considered and bilateral percutaneous nephrostomy or bilateral ureteric stents (if feasible) are advisable for temporarily drainage. Patients may need urgent and transitory dialysis.

Neoureterocystostomy after a prostate ablative procedure may be adequate for definite ureterovesical junction obstruction resolution.

7.2 Watchful waiting

Watchful waiting (WW) is an appropriate strategy for men who are not bothered by their symptoms and have not developed BPH related complications.

This option should include education, reassurance, periodic monitoring and lifestyle advice to the patient. Lifestyle counseling include: reduction of fluid intake during specific times for control of urinary frequency (e.g. at night or when going out in public) but not of the

total amount of daily fluid (above 1500 mL per day), avoidance of alcohol and caffeine because they have diuretic and irritant effect, bladder retraining to increase its capacity and constipation treatment. Watchful waiting is based on the notion that some symptoms may spontaneously improve whilst others may remain stable for years. The PSA level and the prostate volume may be helpful in predicting the risk of acute urinary retention, although they should not be used as a sole determinant for active therapy (Levy and Samraj 2007). Approximately 85% of men will be stable on WW at 1 year, deteriorating progressively to 65% at 5 years (Wasson, Reda et al. 1995; Netto, de Lima et al. 1999). This approach is not suitable for men with installed CKD due to bladder outlet obstruction.

7.3 Medical treatment

Medical approaches are not used to treat BPH complications (in which CKD is included). They are used for LUTS relief and for prevention of BPH progression (especially 5 alpha reductase inhibitors - 5-ARI).

7.3.1 Alpha-blockers

Alpha-blockers address the dynamic component of prostatic obstruction by antagonizing the adrenergic receptors responsible for smooth muscle tone within the stroma, prostate capsule and bladder neck, providing the most rapid symptom relief. They include: terazosin, doxazosin, alfuzosin, tamsulosin and silodosin. These drugs have similar efficacy but different patterns of side-effects:

Alpha-Blocker	Dosage	Side-effects
Terazosin	1 mg once a day May increase up to 20 mg a day	Asthenia, hypotension, dizziness, somnolence
Doxazosin	1 mg once a day May increase up to 8 mg once daily	Orthostatic hypotension, fatigue and dyspnea
Alfuzosin	10 mg once a day	Fatigue, edema, rhinitis, headache, upper respiratory tract infection
Tamsulosin	0,4 mg once a day	Dizziness, rhinitis, abnormal ejaculation
Silodosin	8 mg once a day 4 mg once a day for men with moderate kidney dysfunction	Diarrhea, headache and commons cold symptoms, nasal congestion, retrograde ejaculation (the most common)

Table 3. Alpha blockers used, dosage and side-effects.

The older, less costly, generic alpha blockers remain reasonable choices. However, these require dose titration and blood pressure monitoring. Alpha-blockers are the most prescribed medications for BPH as long as they have a rapid (symptoms may improve in 48 hours) and significant improvement on LUTS.

7.3.2 5-alpha-reductase inhibitors

5-Alpha-Reductase Inhibitors (5-ARI) are anti-androgenic hormonal agents that address the static component of BPH by reducing the prostate volume (up to 20-30%). They include

finasteride and dutasteride and are more effective in prostates larger than 40 mL (Boyle, Gould et al. 1996). According to some trials, finasteride significantly reduced acute urinary retention and the need for surgical treatment in men with BPH.

5-ARIs are the only pharmacologic treatment that may be used to prevent progression of LUTS secondary to BPH and to reduce the risk of urinary retention and future prostate-related surgery. Therefore, indirectly, it may be useful in preventing BPH complications such as chronic kidney failure. However, they can't revert CKD related to BPH after installed.

5-Alpha-Reductase Inhibitor	Dosage	Side-effects
Finasteride	5 mg once a day	Erectile dysfunction, decreased libido, decreased serum PSA, gynecomastia
Dutasteride	1 mg once a day May increase up to 8 mg once daily	

Table 4. 5 alpha-reductase inhibitors used, dosage and side-effects.

Finasteride inhibits exclusively the 5-AR type II isoenzyme, while dutasteride inhibits both types I and II. This difference in activity leads to a reduction in serum levels of dihydroxytestosterone (DHT) by approximately 70% with finasteride compared to approximately 95% with dutasteride (Clark, Hermann et al. 2004).

Finasteride (and probably dutasteride) is an appropriate and effective treatment alternative in men with refractory hematuria presumably due to prostatic bleeding (Foley, Soloman et al. 2000; Kearney, Bingham et al. 2002; Perimenis, Gyftopoulos et al. 2002).

7.3.3 Combination therapy

The Medical Therapy of Prostate Symptoms (MTOPS) Study demonstrated that in the long term, among men with larger prostates, combination therapy is superior to either alpha-blocker or 5-ARI therapy in preventing progression and improving symptoms (McConnell, Roehrborn et al. 2003).

7.3.4 Phytotherapy

The use of plant-derived agents (*Serenoa repens* or Saw palmetto, *Pygeum africanum*) on LUTS and BPH has been popular in Europe for many years and has recently spread in the USA. Their mechanism of action is still unclear. However they seem to improve urinary symptoms without important side effects. In some studies the efficacy of these compounds was found to be equivalent to 5-ARIs and alpha-blockers (Lowe 2001; Debruyne, Koch et al. 2002). The most widely studied and used, *Serenoa repens*, has no effect on prostate volume or the PSA test, but slightly decreases the prostate epithelium. It does not cause erectile dysfunction, but the herb may aggravate chronic gastrointestinal disease such as peptic ulcer (Bent, Kane et al. 2006).

7.4 Surgical treatment

Men who develop serious complications from BPH should be treated surgically in most of the cases. Both Agency for Health Care Policy and Research and International Consensus

Guidelines recommend surgery if the patient has refractory or recurrent urinary retention (failing at least one attempt of catheter removal) or any of the following conditions clearly secondary to BPH: recurrent UTI, recurrent gross hematuria, bladder stones, renal insufficiency, or large bladder diverticula (McConnell, Barry et al. 1994) (Denis et al., 1998). Studies suggest that dialysis dependent patients may recover renal function up to a year after prostatic surgery. In this setting, efforts should be made to identify and treat BPH in patients under dialysis.

Surgeries are associated with postoperative risks such as erectile dysfunction (4% to 10% incidence) and urinary incontinence (0.5% to 1.5%) (Flanigan, Reda et al. 1998) (McConnell, Bruskewitz et al. 1998). The 5-year recurrence rate of BPH following surgery is 2% to 10%(Flanigan, Reda et al. 1998). Proper therapy can be offered to the right men and the costs of long-term renal damage and post-surgical complications can be avoided.

7.5 Standard surgical procedures

TURP (transurethral resection of the prostate) is the hallmark of the urologist, the one against which other therapeutic measures are compared. It takes 20 to 30 minutes to resects an average gland weighing of 30 g and carry risks complications like bleeding, infections, retrograde-ejaculation, hospital stay, impotence and incontinence.

In patients presenting with renal failure due to bladder outflow obstruction, TURP restores normal voiding pattern in many cases. However renal failure due to bladder outflow obstruction tends to be more refractory and 57% of patients in Thomas *et* al. study were dialysis dependent after surgery. Only 3 of 14 patients experienced return to normal renal function post TURP (Thomas, Thomas et al. 2009).

Mortality following prostatectomy has decreased significantly within the past two decades and is less than < 0.25% in contemporary series (Holman, Wisniewski et al. 1999; Hahn, Farahmand et al. 2000). The risk of a TUR-syndrome (fluid intoxication, serum Na+<130 nmol/L) is in the range of 2%. Risk factors for the development of the TUR-syndrome are excessive bleeding with opening of venous sinuses, prolonged operation time, large glands and past or present smoking.

Open prostatectomy is the treatment of choice for large glands (>80-100 mL), bladder stones or if resection of bladder diverticula is indicated. Open prostatectomy involves the surgical removal (enucleation) of the inner portion of the prostate via a suprapubic or retropubic prostatectomy.

7.6 Minimally invasive surgical therapies

Standard operations are *TURP* in small (≤80-100mL) or open prostatectomy in large prostates (>80-100mL). Minimally invasive, alternative surgeries may be considered in selected men and offer advantages regarding risk of bleeding, duration of catheterization, or maintenance of sexual function. (Gabuev and Oelke 2011).

*Transurethral incision of the pro*state (TUIP) or bladder neck incision is recommended for smaller gland (weigh <25g) and has been found to be less invasive than TURP (Orandi 1990). TUIP has several advantages over TURP, such as a lower incidence of complications,

minimal risk of bleeding and blood transfusion, decreased risk of retrograde ejaculation, shorter operating time and hospital stay, and an importantly higher long-term failure rate.

*Transurethral electrovaporiz*ation (TUVP) is a modification of TURP and TUIP, employing high electrical current to vaporize and coagulate the obstructive prostate tissue. Long-term efficacy is comparable with TURP, but high number of patients has been found to experience irritative side effects (Desautel, Burney et al. 1998).

Transurethral needle ablation (TUNA) is a simple and relatively inexpensive procedure which uses a needle to deliver high-frequency radio waves to destroy the enlarged prostatic tissue. TUNA is a successful treatment for small-sized gland and it poses a low or no risk for incontinence and erectile dysfunction (Ramon, Lynch et al. 1997).

*Transurethral microwave thermother*apy (TUMT) heats the prostate using a microwave antennae mounted on a urethral catheter (Thorpe and Neal 2003). TUMT has been found to be safe and cost effective, with reasonable improvement in urine flow rate and minimal impairment on sexual function (Richter, Rotbard et al. 1993).

Transurethral ethanol ablation of the prostate (TEAP) has been recently introduced as a minimally invasive alternative treatment for patients with BPH. TEAP produces necrotic effect on prostatic tissues, leading to fibrosis and shrinkage. It is an effective minimally invasive treatment option for medically high-risk symptomatic patients with BPH that can be performed as an outpatient procedure under regional anesthesia (El-Husseiny and Buchholz 2011).

Laser prostatectomy: four types of lasers have been used to treat LUTS, namely neodymium: yttrium-aluminum-garnet (Nd: YAG) laser, holmium YAG laser (Ho:YAG), potassium titanyl phosphate (KTP), and diode laser. It has been found to be safe and effective technique, with significant improvement in urinary flow rates and symptoms. Short surgery time, shorter catheter use, minimal blood loss and fluid absorption, decreased hospital stay, low erectile dysfunction rates, and bladder neck contractures are few of the advantages of laser prostatectomy over the TURP and other conventional techniques (Donovan, Peters et al. 2000; Bent, Kane et al. 2006). Laser surgery is specially indicated in patients receiving anticoagulant therapy that want to maintain ejaculation or are unfit for TURP.

Transrectal HIFU (high intensity focus ultrasonography) therapy is the only technique that provides non-invasive tissue ablation; however, general anesthesia or at least heavy intravenous sedation is required. Long-term efficacy is limited, with a treatment failure rate of approximately 10% per year.Significant increase in uroflow and a decrease in postvoid residual volume have been observed, but the cost is three times higher than that of TURP (Madersbacher, Kratzik et al. 1993).

8. Future approaches to BPH

Increasing average life expectancy, especially due to better health care and better education of the population, make us believe that soon we shall have, seek for medical care, a greater number of people suffering from elderly diseases. The health burden of disorders such as BPH will be a major dome for research in the future.

Recent investigation is underway in this field, some basic and translational research is being done, in an attempt to better understand and treat this prevalent disease.

Recently Woo *et.* al reported the use of a Prostatic Urethral Lift (PUL) procedure, which is a novel, minimally invasive treatment for symptomatic benign prostatic hyperplasia (BPH). PUL aims to mechanically open the prostatic urethra without ablation or resection, with patients reporting sustained symptom relief for 12 months with minimal morbidity (Woo, Chin et al. 2011).

Tadalafil and other phosphodiesterase type 5 (PDE5) inhibitors have demonstrated beneficial effects on smooth muscle relaxation, smooth muscle and endothelial cell proliferation, nerve activity, and tissue perfusion that may impact LUTS (Andersson, de Groat et al. 2011). Consistent evidence of improvements in LUTS has been shown with PDE5-Is, either alone or in combination with α-blockers (Martinez-Salamanca, Carballido et al. 2011). However, urodynamic results or objective measures of urinary flow are lacking (Martinez-Salamanca, Carballido et al. 2011).

De Souza *et* al, investigated the effects of *Orbignya speciosa*, a nanoparticle extract, newly developed phytotheraphy that can be safely used on the management of BPH (de Souza, Palumbo et al. 2011).

In our country (Portugal) a recent study led by Pisco *et*. al, aimed to evaluate whether prostatic arterial embolization could be a feasible way to treat lower urinary tract symptoms associated with benign prostatic hyperplasia. Their preliminary results and short-term follow-up suggest good symptom control without sexual dysfunction associated with a reduction in prostate volume (Pisco, Pinheiro et al. 2011).

Rick *et* al, in recent times used growth hormone-releasing hormone (GHRH) in animal models. They concluded that GHRH antagonists can lower prostate weight in experimental BPH with significant reductions in protein levels of IL-1β, NF-κβ/p65, and cyclooxygenase-2 (COX-2), suggesting that GHRH antagonists should be considered for further investigation as therapy for BPH (Rick, Schally et al. 2011)

It is important in a near future to characterize a *clinical phenotype* of BPH; measure disease severity and outcomes; design clinical trials; study concepts for drug therapy, behavioral and lifestyle interventions and additional intervention therapies (AUA 2010).

9. Conclusion

Benign prostatic hyperplasia and chronic kidney disease are two common and prevalent entities in elderly men. It has been reported in several studies that threads of evidence suggest that BPH is a risk factor for chronic kidney disease. An average of 13,6% patients presenting to urologic clinics for the treatment of BPH had renal failure. The low occurrence of CKD in BPH clinical trials should not be used to infer a weak association between these two disease processes (Rule et al., 2005). From our own experience we deem that the average of patients with BPH and some degree of renal disease can be higher, mostly because older men most of the times ignore their micturition problems and seek for clinical help just in a later degree of BPH.

Although BPH is not a life-threatening condition, the impact BPH on quality of life (QoL) can be significant and should not be underestimated. On the other hand CKD is an important medical problem that can even be critical (Fox, Larson et al. 2004)

It has been well documented that bladder outlet obstruction by an enlarging prostate can lead to renal insufficiency. Relationship between symptoms severity and elevated serum creatinine in men with BPH have not been well defined. Recent data make us believe that combination of all these factors leading to chronic and progressive urinary retention, high bladder pressure, ureterohydronephrosis work together causing progressive renal injury. Obstructive process root cellular and physiological changes in bladder muscle and collagen, contribute to a high pressure bladder that perpetuates itself with worsening ability to empty and causing kidney lesions leading to renal failure.

The advent of medical treatment has obviated the need for surgery in many patients with BPH. Men in acute urinary retention or those with urinary tract infection and other BPH-complications, may benefit from more aggressive BPH treatment to prevent renal failure, especially if the conditions are recurrent.

Other kidney risk factors such as diabetes mellitus, cardiovascular disease, hypertension, obesity and dyslipidemia may also be considered in the patient with BPH. Etiology of CKD is often multifactorial and BPH may accelerate the progression of CKD in other disease processes.

Older men with BPH often tolerate and ignore lower urinary tract symptoms and may not present for medical consultation until they develop uremic syndrome. Thus, these patients should have prostatic obstruction considered during evaluation and treatment as this diagnosis can be easily missed in unreported LUTS. Close follow-up is mandatory.

We emphasize that CKD secondary to BPH is a preventable disease, and if early detected can prevent costs of CKD treatment (including hemodialysis) with considerable saves (economic, health care, social).

Findings that we mentioned in this chapter suggest that progressive nephropathy caused by prostatic/bladder outflow obstruction – urinary outflow obstruction – might be averted by more adequate screening of renal function in men with untreated BPH.

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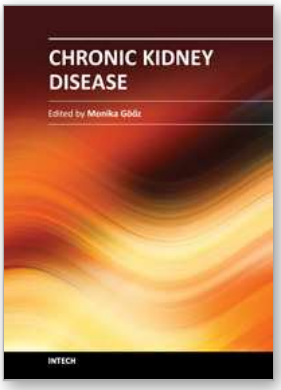

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Chronic kidney disease is an increasing health and economical problem in our world. Obesity and diabetes mellitus, the two most common cause of CKD, are becoming epidemic in our societies. Education on healthy lifestyle and diet is becoming more and more important for reducing the number of type 2 diabetics and patients with hypertension. Education of our patients is also crucial for successful maintenance therapy. There are, however, certain other factors leading to CKD, for instance the genetic predisposition in the case of polycystic kidney disease or type 1 diabetes, where education alone is not enough.

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