UroToday International Journal®

Lower Urinary Tract Symptoms and Benign Prostate Hyperplasia

Ricardo Leao, Bruno Pereira, Hugo Coelho

Submitted August 6, 2012 - Accepted for Publication September 12, 2012

ABSTRACT

Objectives: This article's purpose is to review and discuss the relationship between urinary tract symptoms (LUTS) and renal damage, bearing in mind the epidemiology and pathophysiology of benign prostatic hyperplasia (BPH) and potential association.

Methods: Concerning the increasing number of elderly patients in urology clinics and the incidence of LUTS, the relationship between renal damage and LUTS should be an important issue. The authors searched literature in PubMed in order to correctly identify the pathophysiology and clinical correlation connecting these 2 entities.

Results: BPH is a common disease in adult men and its incidence is age related. Clinical BHP usually refers to the palpable enlargement of the prostate, which can be detected by physical or imaging examination, or by the presence of urinary symptoms loosely defined as LUTS. Despite the many possible causes of obstructive kidney disease, in studies of elderly patients with acute renal failure, the most common cause among all patients was BPH. Considering the high prevalence of BPH in older men with chronic kidney disease (CKD) it is invaluable to take into consideration the relationship between these 2 clinical entities.

Conclusion: Clinical and scientific findings show a worrisome and undiagnosed number of silent urinary obstruction symptoms that can lead to renal damage. This paper emphasizes that renal damage secondary to BPH, clinically manifested by lower urinary tract symptoms, is a preventable disease and must be under the care of physicians.

INTRODUCTION

TBPH is a highly prevalent clinical entity. Based on 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 [1].

BHP is, theoretically, the detection of prostatic hyperplasia 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 the presence of urinary symptoms roughly defined as lower urinary tract symptoms (LUTS) [25].

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) is the continuing significant irreversible reduction in nephron number normally resulting in end-stage renal disease (ESRD). Despite the many possible causes of obstructive kidney disease, in studies of elderly patients with acute renal failure, the most common cause among all patients was BPH [45,23]. Kumar et al. showed in their studies that acute renal failure in patients with obstructive kidney disease was due to BPH (38%), neurogenic bladder (19%), and obstructive pyelonephritis (15%) [23]. Attending to a high prevalence of BPH in older men with CKD, it is invaluable to take into consideration the relationship

KEYWORDS: Benign prostate hyperplasia (BPH), chronic kidney disease (CKD), lower tract urinary symptoms (LUTS), renal disease

CORRESPONDENCE: Ricardo Leao, MD, Department of Urology and Renal Transplantation, University Hospital Center, Quinta dos Vales, Sao Martinho do Bispo, Coimbra, Portugal (romaoleao@gmail.com)

CITATION: *UroToday Int J*. 2012 December;5(6):art 56. http://dx.doi.org/10.3834/uij.1944-5784.2012.12.01

between these 2 clinical entities. However, despite the high prevalence of CKD and BPH in elderly men, there is limited knowledge on the association between these 2 conditions.

METHODS

The main objective of this review is based on the understanding of physiological and cellular mechanisms by which BPH can evolve into CKD. Thus, this paper results from a structured and comprehensive literature review. Searches were done at PubMed. Initial search terms were BPH and CKD. Based on the results of these initial searches, additional, separate searches were performed using the terms such as LUTS, renal disease, renal damage, and acute renal failure. The reference section in published articles was also examined and compared with electronic search results to maximize the review and inclusion of pertinent data. Other comorbidities (diabetes, hypertension) that can cause CKD, and others that can cause lower urinary tract symptoms (overactive bladder activity, neurologic diseases), were not evaluated in this paper.

RESULTS

Epidemiology: Benign Prostatic Hyperplasia

BPH is characterized by the non-malignant overgrowth of prostatic tissue surrounding the urethra, ultimately constricting the urethral opening and giving rise to associated LUTS [44,29,46], and defined by some authors as an important medical problem [5]. The diagnosis of BPH is made based on histologic examination of 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 [9]. BPH is considered a disease of the 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 [47]. It is striking that the age-specific autopsy prevalence is remarkably similar in all populations studied, regardless of ethnic and geographic origin [3]. 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 [29,8]. According to the World Health Organization, although the death rate attributable to BPH is negligible, the estimated DALYs (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 are quite considerable. Most of the disability is probably due to severe clinical symptoms and/or late complications of BPH such as renal failure [32].

Benign Prostatic Hyperplasia and Chronic Kidney Disease

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 the degradation of renal function over time [11]. In a retrospective study of 19 patients admitted for renal dialysis units for end-stage renal disease that was caused by BPH [38,39], the role of BPH as a cause for CKD was highlighted, and a more adequate screening of renal function in men with untreated LUTS was suggested [38]. More recently, a cross-sectional survey in Spain of 2 000 randomly sampled men showed a 2.4% prevalence of self-reported renal failure related to a prostate condition (9% reported renal failure from any cause) [19,34]. Another study [16] 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 non-prostate surgery. Other statistical studies revealed that 13.6% of men who presented for BPH treatment exhibited renal failure [27].

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 [36,37]. More recently, evidence of association between BPH and CKD has also arisen in 2 different studies [18,48]. Bladder outlet obstruction (BOO) signs and symptoms (maximum urinary flow rate (Qmax); post-void residual volume, and obstructive LUTS) are significant predictors [36,48]. BOO probably makes the bridge between CKD and BPH [18]. Most likely this is the reflection of the etiology of CKD secondary to BPH.

As we consider all this data, one should consider that BPH is an almost ubiquitous condition in the older man. Thus, the low occurrence of CKD in BPH clinical trials should not be used to infer a weak association between the 2 disease processes.

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 hypotheses that BPH may result from a reawakening of embryonic induction processes in adulthood [29,30]. The most common renal pathology finding in men with obstructive nephropathy due to BPH is chronic interstitial nephritis [7,38], and 30% of cases have been attributed to obstructive kidney disease. Late or end-stage renal failure secondary to prostatic enlargement or BOO should be amenable to prevention if cases are recognized early; however, it is still difficult to recognize which men with BPH are at risk of renal failure and need close investigation.

Lower Urinary Tract Symptoms (LUTS)

LUTS are clinical criteria to define a urinary dysfunction. Most of the men with BPH have voiding dysfunction, and they complain of nocturia, urgency, weak urinary stream, increased urinary frequency, and a sense of incomplete bladder emptying

UIJ / Vol 5 / Iss 6 / December / http://dx.doi.org/10.3834/uij.1944-5784.2012.12.01 ISSN 1944-5792 (print), ISSN 1944-5784 (online)

after micturition. For many years some studies were done to achieve a scientific relation between LUTS and CKD [16,31]. A retrospective study did not find any relation between the duration of symptoms and serum creatinine levels [16]. Likewise, Gerber et al. did not achieve any success in linking serum creatinine levels and LUTS [12]. However, Hong et al. reported that obstructive symptoms were significantly associated with CKD status [18].

Patient perceptions are receiving greater emphasis as part of clinical decision-making [17,20,35] in daily clinical practice. The variability of the relationship between symptom severity and its impact in GFR requires further investigation [14]. It must take into account that the absence of LUTS in older men does not necessarily exclude BPH with urinary outlet obstruction, and that the severity of LUTS 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 [39]. 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. As such, under-reported symptoms can induce a significant bias in most of studies already done.

Clinical Contributors for LUTS in BPH and Its Relation with CKD

Prostate Enlargement

BPH/BPE (benign prostate enlargement) first develops in the periurethral transition zone of the prostate. Prostate enlargement involves an increase in the number of glands, particularly the periurethral glands, and an increase in smooth-muscle and connective tissue in the periurethral region of the prostate [28,38,47]. Prostate size can be estimated by digital rectal examination (DRE) (underestimating true prostate size), but reliability across observers is, in general, considered [47]. For these reasons, in all cross-sectional studies, prostate volume is assessed by TRUS (transrectal 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. Authors like Shapiro et al. emphasize the role of prostatic smooth muscle in pathophysiology of BPH [41]. Active muscle tone in the human prostate is regulated by the adrenergic nervous system [40], and α-adrenergic blockade leads to a significant down-regulation of normal protein gene expression, specifically smooth-muscle myosin heavy chain [4,47]. Recent studies related prostate size and LUTS in BPH. Hassanzadeh et al. found a significant correlation between urgency and prostate size [15], which can be considered a predictive factor for the disease and possible link between BPE and CKD. The prostate and its enlargement can contribute to outflow obstruction, not only by its static component (periurethral compression caused by a stromal component) but also its dynamic component (smooth-muscle cells and adrenergic pathway).

Post-voiding Residual Urine Volume: Chronic Urinary Retention

Chronic urinary retention is thought to be the dominant mechanism by which BPH can cause renal injury [36]. Rule et al. defined chronic urinary retention (CUR) as post-void residual urine (PVR) higher than 100 mL, and reported that CUR was significantly associated with CKD in community-dwelling men [37]. For years it has been described that large volumes (> 300 mL) affect renal function in advanced BPH [37,48], and PVR of the patients with CKD was significantly greater than that of the patients without CKD. 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 cutoff of 12 ml for PVR [48], and they confirmed PVR as a significant and independent risk factor for CKD. This study showed for the first time that patients with BPH could develop impaired renal function with small amounts of post-void urine (PVR < 100 ml). These findings indicated a higher prevalence of CKD in patients with BPH, acknowledging it as a risk factor for CKD.

Although, as Yamasaki et al. demonstrated, low post-void residual urine can cause the deterioration of renal function, and it is scientifically accepted that, in cases of renal function deterioration, a greater volume of residual post-void urine is observed [48]. PVR cannot be dissociated from changes in bladder remodeling and consequent changes in static component (as it is described in "Bladder Remodeling").

Acute Urinary Retention

Acute urinary retention (AUR) is defined as an acute complication of benign prostatic hyperplasia. AUR represents an immediate indication for intervention or even surgery. Between 25 and 30% of men who underwent transurethral resection of the prostate (TURP) had AUR as their main indication [47]. This complication is not exclusive for patients suffering from BPH. Other causes can trigger acute urinary retention such as surgery, anesthesia, trauma, medications, medical examination, and urinary tract infections (mainly prostatitis). Acute urinary retention is responsible for the majority of acute renal failure cases due to obstructive kidney disease [33] and for long-term tubular dysfunction [36,37].

Bladder Remodeling: A Response to Urinary Obstruction

The bladder has a central role in the pathophysiology of BPH and its complications.
Current evidence suggests that the bladder´s response to

obstruction is largely an adaptive one, although it is only partially adaptive. 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 outflow obstruction directly.

There are of 2 types of bladder changes. First, ones 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, and increased residual urine) and detrusor failure [47]. The development of bladder-wall thickening (easily measurable by ultrasound) and trabeculation due to smooth-muscle hypertrophy and connective tissue permeation are responsible for increased bladder pressure in patients with high-pressure chronic retention [21,37,42]. Severe trabeculation is related to significant residual urine, suggesting that increased collagen in the bladder wall is probably responsible for incomplete bladder emptying rather than impaired muscle function [47]. Detrusor hypertrophy is one of the first modifications in the bladder. Obstruction also induces changes in smooth-muscle cell contractile protein expression, impairing cell-to-cell communication [24,26] that leads to detrusor instability, and, in some cases, to impaired contractility.

Cellular and physiological changes in bladder muscle and collagen contribute to a high-pressure bladder that perpetuates itself with worsening ability to empty, causing kidney lesions. These mechanisms of bladder remodeling 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 [6]. Low bladder compliance and detrusor instability may be causal mechanisms for renal failure in men with chronic urinary retention [37].

Bladder remodeling is a response to continued bladder obstruction, and detrusor smooth-muscle cell is a key contributor to the complex symptoms associated with prostatic obstruction, namely in LUTS/BPH/BPE.

Ureterovesical Junction and Upper Tract Dilation

In general, ureterovesical junction obstruction caused by bladder remodeling in chronic urinary retention is a contributing mechanism for renal failure in BPH [37]. Upper tract dilation occurs because of continued bladder outlet obstruction and remodeling (detrusor hypertrophy and scarring), leading to anatomical ureterovesical junction obstruction [21]. Upper urinary tract dilation or hydronephrosis is consistent with chronic renal failure from obstructive kidney disease [43]. In men with BPH and increased serum creatinine, hydronephrosis is common (one-third), and it is found in 90% of men with BPH who are hospitalized for uremic symptoms [39]. A history of enuresis, painless chronic retention, and palpable bladder should suggest a diagnosis of high-pressure chronic retention with attendant risk of hydroureteronephrosis [39].

Other Causes

Recurrent urinary tract infections in men with chronic urinary retention due to BPH may also contribute to chronic renal failure [37]. Secondary hypertension due to chronic urinary retention is also a complication of BPH, leading to hypertensive kidney disease [13]. Nephrogenic diabetes insipidus caused by partial or chronic urinary obstruction can result in renal failure [22]. Other clinical entities such as diabetes and hypertension are independent factors that can lead to CKD [12]. Patients with BPH are probable carriers of these pathologies that are likely to seriously aggravate renal function and must be taken into account as likely precursors of conditioners of renal disease.

DISCUSSION

Benign prostate hyperplasia and chronic kidney disease are 2 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% of 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 2 disease processes [36]. However, a number of patients with BPH and some degree of renal disease can be higher, mostly because older men mostly ignore their micturition problems and seek clinical help while at a higher degree of BPH.

Although BPH is not a life-threatening condition, the impact of BPH on QoL is significant and should not be underestimated. Concomitantly, CKD can be a critical medical problem [10]. It has been well documented that BOO by an enlarged prostate can lead to renal insufficiency. Recent data suggests that the combination of several factors can lead to chronic and progressive urinary retention, high bladder pressure, and ureterohydronephrosis working together to cause progressive renal injury. Obstructive processes develop cellular and physiological changes in bladder muscle and collagen, contributing to a high-pressure bladder that perpetuates itself with worsening ability to empty, causing kidney lesions that lead to renal failure.

It must be emphasized that CKD secondary to BPH is a preventable disease, and early detection can prevent the heavy tolls of CKD treatment (hemodialysis included) with considerable economic and social savings. Primary physicians have a very important role in the diagnosis and management of men over 50 or 60 with lower urinary tract symptoms.

Nowadays, the number of patients seeking medical care later in life is increasing. Morbidities and complications of common diseases are growing, as we can observe day by day in urologic clinics. BPH is a prevalent urologic disease, and is a very good example of a treatable disease that is now appearing at clinics with serious complications. The correct evaluation of lower urinary tract symptoms, and their underlying causes, may prevent the development of serious diseases with effects on the patient's health. Most guidelines have abolished the screening of renal function for patients with BPH. The increasing number of patients with BPH complications may suggest a change in the evaluation that general physicians, internists, and urologists should take into account.

The findings mentioned 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 LUTS. It is important in the near future to characterize a clinical phenotype of BPH; measure disease severity and outcomes; design clinical trials; and study concepts for drug therapy, behavioral and lifestyle interventions, and additional intervention therapies [2].

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