International Journal of Impotence Research (2009) 21, 267–274
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0955-9930/09 $32.00
www.nature.com/ijir

REVIEW

Measurement of benign prostatic hyperplasia treatment effects on male sexual function

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Benign prostatic hyperplasia (BPH) is the leading cause of lower urinary tract symptoms among the aging male population. Epidemiological, pathophysiological and clinical studies indicate that many of these men also suffer from declining sexual function, especially those undergoing treatment for their BPH-related urinary symptoms. Although urinary symptoms and quality of life may improve with BPH therapy, the resulting effects on sexual function vary by medical, surgical and minimally invasive approaches and have not been consistently reported. As comprehensive, validated instruments to measure male sexual function are now available for routine use in the clinical setting, urologists and primary care providers caring for patients with BPH have the opportunity to monitor both urinary and sexual function before, during and after BPH therapy. Herein, we describe the relationship between BPH and its treatments on male sexual function, the role of new measures for sexual functioning and opportunities for future work to improve the care of men suffering from both maladies.
International Journal of Impotence Research (2009) **21,** 267–274; doi:10.1038/ijir.2009.26; published online 18 June 2009

Keywords: BPH; erectile dysfunction; medical therapy; surgery

Introduction

Lower urinary symptoms, secondary to benign prostatic hyperplasia (BPH), and declines in male sexual function are common manifestations of aging, and have been associated with each other in a number of clinical and epidemiological studies.[1–9] In this regard, biological mechanisms have been forwarded[10] and efforts to discern a relationship independent of common risk factors such as age and comorbidity have been made.[8,11,12]

Causality notwithstanding, deterioration in both urinary and sexual function are significant issues contributing to the quality of life in the aging male population.[11,13–15] Moreover, the evolution of instruments to measure lower urinary tract symptoms (LUTS) and sexual function alongside the implementation of medical therapy for BPH has allowed us to better understand how male sexual functioning is altered by therapies for BPH. For example, comprehensive measures of ejaculatory function, quality of life and overall satisfaction have been developed and are useful for comparing various therapies.

In light of the multiple treatments for BPH, that is, medical, surgical and minimally invasive therapies, a better understanding of their individual effects on male sexual function will allow both urologists and the increasing number of primary care providers treating BPH to select the optimal treatment for their patients.

BPH symptoms and therapy

Benign prostatic hyperplasia is the leading cause of LUTS among the aging male population.[9,16] LUTS range from nocturia, urinary frequency and urgency to a decreased and intermittent stream with incomplete bladder emptying, and commonly result in a decreased quality of life.[13,14,16–18] This decreased quality of life and increased bother are often the primary reasons men seek treatment.[18]

For men with mild to moderate urinary symptoms without bother, watchful waiting and behavior modification are recommended as the side effects of medical therapy outweigh potential benefits in

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Received 14 April 2009; revised 19 May 2009; accepted 20 May 2009; published online 18 June 2009

quality of life.[16,19] As urinary symptoms worsen and become more bothersome, medical therapy with α-adrenergic blockade alone, or in combination with 5-α-reductase inhibitors (for men with larger prostates), are the options.[16] For moderate to severe symptoms that are bothersome, minimally invasive therapy (that is, microwave therapy, transurethral needle ablation) and surgery (transurethral resection, laser ablation or open prostatectomy) are also valid options.[16] However, the latter more aggressive treatment approaches harbor greater potential for impaired sexual functioning and discussion of the potential risks and benefits with the patient are paramount.

The current international standard for measuring the severity and frequency of urinary symptoms secondary to BPH is the International Prostate Symptom Score (IPSS)—a combination of the seven-question American Urological Association BPH Symptom Index[20] and a disease-specific quality of life question.[21,22] This validated instrument consists of seven questions scored from 0 to 5 (0–35) in an increasing order of symptom severity (for example, urinary frequency, nocturia, bladder emptying) and an assessment of bother, that is, living the rest of your life with your current symptoms. The IPSS addresses BPH-related urinary symptoms and quality of life due to these symptoms, however it does not speak of any of the commonly coexisting male sexual function deficits related to BPH and its treatments.

Epidemiological, pathophysiological and clinical support of BPH and male sexual dysfunction relationship

Although studies conflict regarding a causal relationship between BPH-related urinary symptoms and declines in male sexual function, associations independent of age and comorbidity have been reported.[8,11,12] In fact, a dose-response relationship between increasing LUTS and worsening sexual function has been found. After accounting for age, a relationship of worsening sexual function with increasing LUTS was revealed in a cross-sectional evaluation of the Olmsted County Study where ejaculatory function and overall problems with sexual function were affected the most (partial correlation coefficients −0.22 and −0.23, respectively).[12] Likewise, in the Cologne Male Survey, worsening erectile function was not only associated with age, but also with worsening LUTS independent of the age-related effects (odds ratio (OR) 2.11, 95% confidence interval CI (1.75–2.55)).[8] In a broader population, the Multinational Survey of the Aging Male (MSAM-7) clearly demonstrated that although both LUTS and sexual dysfunction share the similar risk factors of age and comorbidity, the severity of sexual dysfunction increased with worsening urinary symptoms in an independent manner.[11] For example, the odds of erectile and ejaculatory dysfunction on multivariate analysis increased across all categories of worsening urinary function as measured using the IPSS (mild symptoms, OR 1.98, 95% CI (1.67–2.34), OR 1.64, 95% CI (1.40–1.93), moderate symptoms OR 3.76, 95% CI (3.14–4.50), OR 3.19, 95% CI (2.68–3.78) and severe symptoms OR 7.67, 95% CI (5.87–10.02), OR 6.25, 95% CI (4.78–8.17), respectively). Consistent with prior studies,[1–7] common risk factors for both BPH and sexual dysfunction, that is, increasing age, diabetes, hypertension and so on, were identified in these analyses.

Regarding the declines in sexual function with worsening urinary tract symptoms, these and other studies approach the functional assessment inconsistently. Although the MSAM-7[11] used the gold standard at the time, the International Index of Erectile Function,[23] the Cologne Male Survey[8] used the validated Kölner Erfassungsbogen der Erektilen Dysfunktion[7] instrument, which focuses more specifically on erectile function than on measures of satisfaction and ejaculatory function as in the International Index of Erectile Function (IIEF). In the earlier Olmsted County Study, the five-question sexual function instrument assessed concern about sexual function, ability to achieve erection, frequency of sexual drive, level of satisfaction, and whether sexual function was changing over time.[24] Taken together, these studies support the contention that LUTS and sexual function are related somehow but the lack of consistent, comprehensive measures of male sexual function has hampered its assessment.

How is BPH treatment associated with male sexual function?

Attention to the side effects of medical therapy for BPH symptoms on men's sexual health was heightened after a series of randomized trials showed improvements in urinary function with α-adrenergic receptor blockade (terazosin, doxazosin, alfuzosin and tamsulosin)[25–29] and 5-α-reductase inhibitor therapy[30–32] in the 1990s. Although these treatments delayed or avoided surgery through improvements in urinary symptoms because of prostatic urethral and bladder neck relaxation (α-blockade) and prostate shrinkage from decreased local dihydrotesterone production (5-α-reductase inhibitors), decreasing erectile and ejaculatory function as well as libido were recognized as common side effects. For example, decreasing libido, erectile and ejaculatory function were noted with finasteride and combination therapy (finasteride and doxazosin) in the Medical Therapy of Prostate Symptoms Study.[33] This was an important finding that confirmed explanations regarding the effects of decreased local

dihydrotesterone production in the prostate as well as the more global effects on libido.[34,35] Finasteride and its relative, dutasteride, have both been associated with decreased libido and erectile dysfunction from decreased dihydrotesterone, as well as ejaculatory dysfunction from decreased seminal fluid production.[34–37]

α-adrenergic blockade therapies rarely decrease libido and may even improve overall sexual function while treating urinary symptoms,[38–40] however their effects on ejaculation vary and have been inconsistently measured. Non-selective α-blockade (that is, targeting α_1-adrenergic receptor subtypes in the prostate and bladder neck, as well as vascular smooth muscle[41]) using terazosin has shown marginal worsening of ejaculatory function,[42] although doxazosin may also mildly affect ejaculatory function.[33] To limit the vascular smooth muscle effects of non-selective α-blockade (for example, orthostatic hypotension), selective α-blockade using drugs with increased α_{1A}- to α_{1B}-adrenergic receptor selectivity to preferentially affect the prostate and urethra (for example, tamsulosin),[41] or those with clinical selectivity for the genitourinary tract (for example, alfuzosin),[41] are now commonly used, and likewise may affect ejaculatory function. For example, a dose-dependent effect of tamsulosin exists such that at the most commonly used dose of 0.4 mg, 6% of men may experience ejaculatory dysfunction, whereas at the maximum dose of 0.8 mg, 18% of men may be affected.[43] To compare the effects of tamsulosin (0.4 mg) to alfuzosin (2.5 mg three times daily), one study demonstrated no differences in abnormal ejaculation among the drugs as did another evaluating 0.2 mg tamsulosin versus 10 mg alfuzosin.[44,45] However, in healthy young volunteers, alfuzosin has been shown to maintain ejaculatory function better than maximum-dose tamsulosin, consistent with animal studies.[46,47] Most recently, a pooled analysis of silodosin, another selective α-blocker,[48] showed that 28% of patients experienced ejaculatory dysfunction compared with ~1% for placebo.[49] Despite this and similar to other studies, discontinuation of therapy because of these effects was very low (2.8%). Silodosin's effects seem primarily mediated by anejaculation and failure of emission.[50,51] Hence, these and other studies reveal that α-blockade mechanically affects the expulsion of the ejaculate, unlike the decreased production encountered in 5-α-reductase inhibitor therapy.[52]

The above findings indicate the varied capacities of medical therapy to affect male sexual function during medical treatment for BPH-related LUTS. Recently, the prospective BPH Registry confirmed the varying side effects of BPH medical therapies in a broad-based clinical cohort.[53] As shown in Table 1, the physiologic mechanisms and sexual function deficits associated with each BPH medical therapy vary and need to be considered when selecting a regimen. However, in order to best monitor for potential side effects, clinicians need to use consistent, validated instruments before and during therapy, adjusting the regimen accordingly.

As surgical treatments for BPH evolved toward minimally invasive approaches and the instruments to measure sexual function improved, efforts to understand their effects on male sexual function were furthered.[54] Even early studies measuring treatment outcomes after transurethral resection of the prostate reported on impotence and the obvious ejaculatory deficits after surgery.[55] As electrocautery disrupts the integrity of the bladder neck and potentially scars the ejaculatory ducts, declines in ejaculatory function are extremely common with this approach (>50%),[56] whereas subsequent erectile dysfunction is now rare (<5%).[57] With increasing knowledge of other potential sexual function deficits after surgical treatment, decreased libido and worsened satisfaction with sexuality 1 year after transurethral resection have also been demonstrated.[58]

In this literature, minimally invasive therapies seem to be less frequently associated with erectile or ejaculatory dysfunction.[56,59] The effects of surgical and minimally invasive therapies vary for different aspects of male sexual function (see Table 1). Given that the patient population for surgical therapy is likely to differ from medical therapy (that is, more severe urinary symptoms), minimizing surgical treatment effects on sexual function is necessary while attempting to improve poor urinary function. In addition, better understanding of the manner by which the success of surgical therapy and the irreversible ejaculatory deficits affect the patient's perceptions of their sexual function are areas where prospective research is needed. Specifically, this literature fails to use consistent measures of sexual function before and after surgical therapy.

Evolution of male sexual function symptom and treatment measurement in common clinical settings

Evolving measurement aims have broadened the scope of instruments assessing male sexual function in the studies cited earlier. Indeed, it is now recognized that erectile function is only part of picture, with focus increasing on ejaculatory dysfunction, libido, satisfaction, quality of life and bother.[11,24] Before comprehensive measurement instruments such as the Male Sexual Health Questionnaire (MSHQ),[60] the manifestations of male sexual dysfunction were addressed more in terms of binary outcomes for erectile and ejaculatory function. For example, early studies after transurethral resection of the prostate simply evaluated the presence of impotence (for example, 3–10% following surgery) and the ability to ejaculate (for example, 1/3 of patients) after prostatectomy;[61] however, we

Table 1 The effects of medical, surgical and minimally invasive BPH therapy on male sexual function and lower urinary tract symptoms[a]

BPH Treatment	*Male sexual function*					*Urinary function*	
	Ejaculatory function		*Erectile function*				
	Decreased production	*Anejaculation/retrograde ejaculation*	*Quality of erection*	*Libido/drive*	*Satisfaction*	*IPSS*	*QOL*
Medical therapy							
α-adrenergic blockers							
Doxazosin[b,33,36,40,75,76]	↔	↔↓	↑	↔	↔	↑	↑
Terazosin[b,26,31,42]	↔	↔↓	↔	↔	↔	↑	↑
Alfuzosin[b,32,36,39,44,77,78]	↔	↔↓	↑	↔	↑	↑	↑
Tamsulosin[b,27,36,43,44,77,79–81]	↔	↓	↔	↔	↑	↑	↑
Silodosin[49,51,82,83]	↔	↓↓	n/a	n/a	n/a	↑	↑
5-α-reductase inhibitors							
Finasteride[b,30,32,34,36,71,84–87]	↓	↔	↓	↓	↓	↑	↑
Dutasteride[36,37,88–90]	↓	↔	↓	↓	↓	↑	↑
Combination therapy[b,32,33,36,84]	↓	↔↓	↓	↓	↓	↑	↑
Minimally invasive therapy							
Transurethral needle ablation[b,54,59,91–95]	↔	↔↓	↔	↔	↔	↑↑	↑↑↑
Transurethral microwave heat treatments[b,54,95]	↔	↔↓	↔↓	↔	↔	↑↑	↑↑
Urolume stent (American Medical Systems, Minnetonka, Minnesota)[b,96]	↔	↓	↔	↓	↔	↑↑	↔
Surgical therapy							
Transurethral resection of the prostate[b,54,58,69,70,95,97,98]	↔	↓↓↓	↓↓	↓↓	↓↓	↑↑↑	↑↑↑
Transurethral electrovaporization[b]	↔	↓↓↓	↓↓	↔	↓↓	↑↑↑	↑↑↑
Transurethral incision of the prostate[b,97,99]	↔	↓↓	↓↓	↔	↔	↑↑	↑↑↑
Transurethral holmium laser resection/enucleation[b,54,98,100]	↔	↓↓↓	↓	↓	↓↓	↑↑↑	↑↑↑
Transurethral laser vaporization[b]	↔	↓↓↓	↓↓	↓	↓↓	↑↑	↑↑↑
Transurethral laser coagulation[b,54]	↔	↓↓	↓↓	↓	↓↓	↑↑↑	↑↑↑
Open prostatectomy[b,97]	↔	↓↓↓	↓	↓↓	↓↓	↑↑	↑

Abbreviations: AUA, American Urological Association; BPH, benign prostatic hyperplasia; IPSS, International Prostate Symptom Score; QOL, quality of life.

[a]The therapeutic effects in this table are based on a review of the cited literature. They do not represent a systematic review nor meta-analysis of the effects of BPH therapy on sexual function.

[b]Estimated effect sizes are based on the AUA Guideline treatment outcomes meta-analysis 2003.[52]

↑↑↑ vast improvement, ↑↑ moderate improvement, ↑ slight improvement, ↔ no/minimal change, ↓ slight worsening, ↓↓ moderate worsening, ↓↓↓ severe worsening.

IPSS/AUA Symptoms Index Score: ↑↑↑ vast improvement (−15), ↑↑ moderate improvement (−10), ↑ slight improvement (−5), ↔ no change (0).

Disease-specific Quality of Life Score: ↑↑↑ vast improvement (⩽−3), ↑↑ moderate improvement (−2), ↑ slight improvement (−1), ↔ no change (0).

Erectile dysfunction: ↔ no change (<5%), ↓ slight worsening (5%), ↓↓ moderate worsening (10%), ↓↓↓ severe worsening (15%).

now know much more about the degree to which erectile and ejaculatory function contribute more broadly to overall male sexual function and are affected after BPH treatment.

As erectile dysfunction therapy advanced, the IIEF, a 15-question instrument addressing domains of erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction, was developed and validated by Ray Rosen.[23] To improve its application in the clinical setting, a shorter version of the IIEF, the IIEF-5, was examined and found to be an excellent diagnostic tool to determine the presence and severity of erectile dysfunction.[62] The IIEF-5 focuses on erectile function and satisfaction with intercourse, however does little to quantify other aspects of male sexual function, such as libido, overall satisfaction and relationship issues, that are addressed in the longer form.

Realizing ejaculatory dysfunction and declines in satisfaction were increasingly common, especially in men with BPH-related urinary symptoms, Dr Rosen further sought to develop a more comprehensive state of the art sexual measure. To this end, a multidimensional measure of sexual function and satisfaction, the MSHQ was developed and validated for older men with both sexual dysfunction and LUTS.[60] The two domains of sexual function contain three questions to assess erectile function and seven questions to more broadly gauge ejaculatory function than had been previously done. This measure seeks to better understand ejaculatory function in terms of timing, anejaculation, volume, force, and function relative to 5 years earlier. Importantly, it now appears that ejaculatory function is perturbed not only by surgical but also by medical therapies for BPH. A sexual satisfaction domain rounds out the instrument with six questions assessing communication, affection, quality, frequency, sexual and overall satisfaction with the individual's partner. The complete, validated instrument consists of 25 items and better qualifies the ejaculatory and satisfaction aspects of male sexual dysfunction relative to the IIEF.

Recently, a brief four-question assessment of ejaculatory function and bother, the Male Sexual Health Questionnaire-Ejaculatory Dysfunction Short Form (MSHQ-EjD) was created. Capturing the most bothersome characteristics of ejaculatory dysfunction for older men with urinary symptoms, three functional (frequency, force and volume) and one bother question were included in the instrument.[63] Assessing this instrument relative to the unabridged, seven-item ejaculatory function domain of the MSHQ in multiple clinical populations, including men in the BPH Registry, the MSHQ-EjD correlated well with the parent instrument and was deemed an excellent tool for measuring ejaculatory dysfunction.[63] Consequently, this more-brief measure increases its utility in the clinical setting akin to the IIEF-5. In terms of BPH and its treatments, clinician's now have these two straightforward, validated instruments to readily assess both erectile and ejaculatory function, in addition to the IPSS, for men seeking care.

Future investigation

Now that easily administered, validated instruments are available to measure the prevalence and effects of ejaculatory dysfunction on male sexual function, more research is needed for the prevention of ejaculatory dysfunction, as well as the declines in libido, satisfaction and erectile function when treating men with BPH-related urinary symptoms. To take advantage of potentially common pathophysiological mechanisms,[64] PDE-5 inhibitors have been investigated to improve erectile function as well as urinary symptoms due to BPH.[65,66] Similarly, are there medical therapies to actually improve ejaculatory function[67] and likewise BPH-related LUTS? Investigating the mechanisms by which BPH therapies may actually cause sexual dysfunction could generate opportunities for these prevention strategies to be developed.

In terms of surgical treatments, anecdotal reports suggest that there are subtle techniques for preserving erectile and ejaculatory function but these have not been systematically studied. As transurethral resection of the prostate has evolved, rates of associated erectile dysfunction have decreased, whereas ejaculatory dysfunction remains common.[52,68–70] Addressing this through a better understanding of surgical anatomy and physiology is likely to provide insights into how to better preserve function.

Disseminating the body of knowledge related to the effects of BPH and its treatments on male sexual function to the primary care community will also improve patient care. As primary care providers increasingly care for patients with BPH,[71] better addressing the knowledge discrepancies regarding the underlying sexual side effects of treatment will improve care outside the urology office.[72,73] Moreover, in light of the infrequent discussions of sexual health in older Americans, understanding the hidden BPH treatment effects is even more important for providers as those less likely to discuss their status typically have worse sexual function.[74]

Lastly, investigating a composite measure of male urinary and sexual function, including disease-specific quality of life, that is easy to administer, validated, and shorter than the IPSS, IIEF-5 and MSHQ-EjD Short Form will provide a simple means by which one can assess BPH treatment-related sexual effects. Although some may argue disease-specific measures are best, we now know that lower urinary tract symptoms and declines in male sexual function are interrelated, underdiagnosed, and may

perhaps even share a common pathophysiology. Offering patients a straightforward, comprehensive measure may improve BPH and sexual function care under both the urologist and primary care physician.

Conflict of interest

Dr Wei has funded research by and is a paid consultant for Sanofi-Aventis Pharmaceuticals. He is a consultant and proctor for American Medical Systems. Dr Skolarus declares no potential conflict of interest.

Acknowledgments

This study was supported by an NIH T32 training grant (NIH 2 T32 DK007782-06).

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