Pathogenic mechanisms linking benign prostatic hyperplasia, lower urinary tract symptoms and erectile dysfunction

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Abstract

Introduction: Erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) caused by benign prostatic hyperplasia (BPH) are clinical entities very prevalent in men aged over 50 years. There is evidence that both may have a common pathophysiology.

Objective: The objective of this study was to conduct a literature review aiming to show theories and hypotheses that justify a single pathophysiology for ED and LUTS/BPH.

Methods: A search in Medline using the keywords of the Medical Subject Headings (MESH) 'erectile dysfunction' and 'lower urinary tract symptoms' in all fields of the database up to 15 December 2012. This search found 198 relevant articles that were analyzed.

Results: The data and articles were divided according to the type of evidence found. There are strong epidemiological data showing that LUTS/BPH is a risk factor for developing ED. Several experimental models demonstrated partial obstruction of the bladder in animals causes voiding disorders as well as a negative impact on erectile function of the operated animals. The increased adrenergic tone in animals leads to prostate growth and urodynamic conditions similar to those found in men with LUTS and ED. Arteriosclerosis may lead to loss of vesical complacency, urinary tract obstruction and fibrosis of the cavernous bodies. The use of phosphodiesterase type 5 inhibitors (PDE-5i) and/or alpha-adrenergic blockers to treat ED and LUTS/BPH reinforces the hypothesis that, at least in some patients, both clinical pictures may have the same pathophysiology.

Keywords: erectile dysfunction; lower urinary tract symptoms; benign prostatic hyperplasia

Introduction

Erectile dysfunction (ED) is a very prevalent clinical condition, primarily found in those aged over 40 years. The same applies to lower urinary tract symptoms (LUTS) caused by benign prostatic hyperplasia (BPH).

According to the classic Massachusetts Aging Male Study [Feldman *et al.* 1994], the prevalence of ED is approximately 50% at 50 years, rising to 70% after 70 years. In a study carried out in Japan, Malaysia, Italy and Brazil, Nicolosi and colleagues reported a prevalence of complete or moderate ED of 9% in males aged 40–44 years, achieving 54% in those between 65 and 70 years of age [Nicolosi *et al.* 2003].

The prevalence of LUTS/BPH also rises with age. According to Chute and colleagues, it amounts to

24% among men aged 40–49 years and to 36% in males aged 60–69 years [Chute *et al.* 1993].

This correlation between two clinical entities could be just a statistical fact: two diseases affecting the same age group.

However, there are several indications that make one consider that there might be a pathophysiologic interaction between ED and LUTS/BPH. This review is designed to highlight the evidence for a common pathophysiology, and some of which is still hypothetical.

Methods

A search was performed in Medline using the keywords of the Medical Subject Headings (MESH) 'erectile dysfunction' and 'lower tract

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urinary symptoms' in all fields of the database up to 15 December 2012.

This search resulted in 198 relevant articles that were analyzed. This is not a systematic review and included only data that were significant to the hypotheses and theories showing the pathogenic mechanisms relating LUTS/BPH to ED. In the case of articles with similar design and/or comparable findings, the most significant, according to the authors, were chosen.

Results

The articles and data were separated based on six groups of indications and evidence correlating LUTS/BPH and ED: epidemiologic data; experimental models; increased adrenergic response causing ED and LUTS/BPH; presence of nitrergic innervation in the prostate and cavernous bodies; pelvic arterial insufficiency; and use of the same drugs to simultaneously treat ED and LUTS/BPH.

Epidemiologic data

In all age groups the prevalence of ED is higher in men presenting LUTS [Braun *et al.* 2000]. On the other hand, the prevalence of ED significantly increases as LUTS become more severe [Nicolosi *et al.* 2003].

Several epidemiologic studies assessed thousands of men in all continents and demonstrated that LUTS/BPH is a significant risk factor for ED. For instance, the *National Health and Social Life Survey* reported an odds ratio of 3.13 for LUTS/BPH as risk factor for ED [Laumann *et al.* 1999]. In the DENSA study, conducted in the Northern part of South America, LUTS/BPH appears as a risk factor for ED with an odds ratio of 1.5 [Morillo *et al.* 2002]. In the Cologne Male Survey, the odds ratio of LUTS/BPH as a risk factor for ED was 3.17 [Braun *et al.* 2000]. Ponholzer and colleagues evaluated 2858 men aged 20–80 years (mean age of 45.8 years) and found LUTS/BPH, particularly nocturia and the negative impact on quality of life caused by such symptoms, as independent risk factors for ED [Ponholzer *et al.* 2004]. Seftel and colleagues recently published a systematic review of epidemiologic studies correlating LUTS/BPH and ED [Seftel *et al.* 2013]. They analyzed 23 relevant studies and concluded that roughly one-third of men aged over 50 years present ED and LUTS/BPH simultaneously;

however, among those patients who search medical care for any of these two conditions most suffer from both diseases. They stated that the quality of life indices are worse when LUTS/BPH and ED are present.

In the clinical practice, the International Prostate Symptom Score (IPSS) is a validated instrument to assess LUTS/BPH. Likewise, the Sexual Health Inventory for Men (SHIM), which is the abridged version of the International Index of Erectile Function (IIEF), it is a validated tool to assess erectile function. In numerous articles demonstrated a strong correlation between these two instruments, showing that the worse voiding function, the more impaired erectile function in men aged over 40 years [Glina *et al.* 2006; Nasir *et al.* 2011].

Shiri and colleagues prospectively verified the presence of LUTS/BPH and its impact on quality of life in the incidence of ED in a population of non-ED males, aged 50, 60 and 70 years, residing in Tampere, Finland [Shiri *et al.* 2005]. The individuals answered a questionnaire by mail in 1994 and again in 2005. The population comprised 1126 men who responded to the Danish Prostate Symptom Score and to two questions on ability to achieve and maintain erection. The incidence of ED in the second evaluation rose with presence and severity of LUTS/BPH at baseline. The incidence of ED was 2.7-fold higher in men with a score of 7–11, when compared with men with no LUTS (score 0) and 3.1-fold higher in males with a score of greater than 11. The authors observed the incidence of ED rose by 5% for each score-point increase in LUTS and by 11% for each point in the symptom score for associated LUTS and quality of life.

Experimental models

Several experimental models have been created to study the relation between ED and LUTS/BPH.

Chang and colleagues created an experimental model using a partial obstruction of the vesical neck to establish a LUTS model and identified that operated animals presented an increased tonus at baseline in the smooth muscle of the cavernous body, associated to an elevated level of myosin phosphorylation in smooth muscles [Chang *et al.* 2005]. Moreover, they observed increased activity of kinase and reduced activity of phosphatase in cell extracts of the cavernous body isolated in animals with partial obstruction

of the bladder. Finally, they reported increased expression of two isoforms of Rho-kinase (alpha and beta). Increased basal phosphorylation, which is required for smooth muscle contraction, mediated by higher expression and activity of Rho-kinase, would make the smooth cavernous muscle more resistant to relaxing and, consequently, would hinder erection. This could be the explanation for LUTS/BPH and ED coexisting.

Gur and colleagues also studied how partial vesical obstruction, through partial ligation of the urethra, can affect the erectile function of rats [Gur *et al.* 2008]. They studied animals *in vivo* by monitoring the relation between intracavernous pressure and mean arterial pressure, and also evaluated the isolated muscle fibers in organ-bath studies. The authors verified that rats with partial obstruction of the bladder had lower erectile responses as compared with control animals. On the other hand, the smooth muscle fibers of the operated animals showed less relaxation in response to electrical stimuli to acetylcholine, as well as less contraction induced by phenylephrine. An immunohistochemical study demonstrated decreased expression of neuronal nitric oxide synthase (nNOS) and increased protein expression of the endothelial nitric oxide synthase (eNOS) and induced nitric oxide synthase (iNOS) in the muscle fibers of the operated animals. The authors concluded that changes in the erectile function of operated animals occurred due to altered expression and bioavailability of nitric oxide.

In a study by Kobayashi and colleagues, the partial obstruction of the bladder neck in rats led to significant worsening of voiding with increased postvoiding residue and reduced efficiency of vesical contraction [Kobayashi *et al.* 2011]. Assessing the erectile function by means of intracavernous and arterial pressure during electrical stimulation of the cavernous nerve was dramatically hindered 16 weeks after creating the obstruction. Moreover, the expression of eNOS in the cavernous body was diminished significantly, showing again that, at least in rats, urinary obstruction can affect the production of nitric oxide in the penis and, consequently, the erectile function. In a similar model but using rabbits, Lin and colleagues demonstrated that partial obstruction of the bladder results in progressively increased expression of TGF beta 1 in the penis, as early as 2 weeks after obstruction [Lin *et al.* 2012]; in addition, the authors detected the presence of oxidative stress biomarkers in the penis of

animals with vesical obstruction when compared with control animals.

Increased adrenergic response may cause ED and LUTS/BPH

Both urinary function and erection can be affected by changes in the smooth muscle tonus caused by increased adrenergic response. Unilateral sympathectomy in rats led to homolateral increase in prostate [McVary *et al.* 1994]. Transgenic rats that are spontaneously hypertensive due to greater adrenergic tonus presented urodynamic characteristics similar to those of males with LUTS (reduced vesical intercontraction interval and decreased urinary output, and increased nonvoiding contractions). Furthermore, the rats presented a deficient erectile response to electrical stimulus of the cavernous nerve [Oudot *et al.* 2012].

Presence of nitrergic innervation in the prostate and cavernous bodies

Some authors [Bloch *et al.* 1997; Kedia *et al.* 2008] demonstrated there is intense nitrergic innervation in the prostate glandular epithelium, fibromuscular stroma and blood vessels of normal gland; this innervation is diminished in BPH. On the other hand, the importance of nitric oxide in maintaining erectile function is well known [Andersson, 2001].

Lee and colleagues studied a population of 372 men from Taiwan and found that polymorphism of eNOS gene G894T is more frequent in males presenting ED and LUTS/BPH [Lee *et al.* 2009]. Such polymorphism was described in exon 7 of the eNOS gene, which encodes the enzymes that produces endothelial nitric oxide. This polymorphism causes a change in the amino acid sequence, resulting in altered activity of the enzyme and reduced production of nitric oxide [Bivalacqua *et al.* 2003]. This finding shows that there may even be a genetic origin for the association between ED and BPH/LUTS.

Pelvic arterial insufficiency

Arteriosclerosis is very frequent in elderly men, and pelvic arterial insufficiency causing hypoxia could increase the expression of transforming growth factor (TGF) beta of fibroblasts and interfere in the production of prostanoids, replacing the penile, vesical and prostate smooth muscles by collagen and fibrosis. These changes

may result in loss of vesical complacency, obstruction of urinary flow and hinder relaxation of cavernous sinusoidal smooth muscles, leading to LUTS/BPH and ED. [Tarcan *et al.* 1998].

El-Sakka assessed 374 men with ED, using the IIEF and Doppler ultrasonography of the cavernous arteries to consider possible vascular causes for sexual dysfunction [El-Sakka, 2005]. All patients responded to the IPSS to assess the presence of LUTS/BPH. The mean age of the men was 54.8 years (range of 24–84 years). The author found a significant association between the presence of LUTS/BPH and reduced systolic peak velocity, which is an indirect sign of penile arterial insufficiency.

Use of the same medications to simultaneously treat ED and LUTS/BPH

The phosphodiesterase type 5 inhibitors (PDE-5i) are the first choice to treat ED and they act by increasing availability of cyclic GMP in the cavernous body, facilitating relaxation of smooth muscle and, consequently, erection. Tinel and colleagues confirmed the expression of PDE-5i in the lower urinary tract of rats and their action on the urethra, prostate and bladder of such animals [Tinel *et al.* 2006]. They studied the expression of messenger RNA (mRNA) of PDE-5i in the lower urinary tract of rats, the action of these isolated muscle fibers in the bladder, urethra and prostate, in addition to considering the action of sildenafil and vardenafil in the vesical function of animals with partial obstruction of the vesical neck. The greater concentration of PDE-5i mRNA was found in the bladder, followed by the urethra and prostate. The authors observed that sildenafil, tadalafil and vardenafil reduced dose-dependent contraction of the muscle fibers of the three studied organs, and both sildenafil and vardenafil given by parenteral route in a single dose diminished noninhibited contractions in animals with partial obstruction of the bladder.

Oger and colleagues verified the action of sildenafil [Oger *et al.* 2009] and of tadalafil [Oger *et al.* 2010] in muscle fibers of human prostate and penile tissues, obtained from surgical specimens and observed that the two drugs have a relaxing effect in both tissues.

A recent study has demonstrated again that tadalafil enables relaxation of isolated prostate smooth muscles [Angulo *et al.* 2012]. Zhao and colleagues

studied men with LUTS/BPH submitted to endoscopic resection of the prostate, who received a single dose of tadalafil and udenafil 1 hour before surgery, and found the concentration of both PDE-5i was significantly higher in prostate tissue than in plasma, and both significantly raised the AMP and cyclic GMP levels in the plasma and prostate tissue [Zhao *et al.* 2011]. Recently, Minagawa and colleagues, in an experimental work, showed that systemic administration of tadalafil to rats reduced the mechanosensitive response of nervous fibers induced by vesical distension; moreover it inhibited activity by intravesical instillation of acrolein [Minagawa *et al.* 2012]. Despite this experimental evidence that PDE-5i acts in the lower urinary tract of animals, a full explanation of its mode of action in the prostate remains outstanding.

There are more clinical clues. Bertolotto and colleagues administrated 20 mg of tadalafil in 12 patients with BPH, 90 minutes before performing transrectal Doppler sonography with contrast injected [Bertolotto *et al.* 2009]. The images showed increased perfusion of the prostate with the use of PDE-5i. There is more evidence that this class of drugs has a positive impact on LUTS/BPH. In a systematic review of the literature, Gacci and colleagues demonstrated the use of PDE-5i was associated to a significant improvement in the IIEF and in the IPSS, but it was not related to voiding flow, proving that this drug class can treat both ED and LUTS/HBP [Gacci *et al.* 2012]. The improvement in LUTS/BPH was also observed and described with sildenafil [McVary *et al.* 2007], vardenafil [Stief *et al.* 2008], tadalafil [Porst *et al.* 2011], mirodenafil [Lee *et al.* 2011], udenafil [Martínez-Salamanca *et al.* 2011] and UK-369.003 [Tamimi *et al.* 2005], showing that it is the action of the drug class. In spite of relieving symptoms, the action of PDE-5i on urinary flow has not yet been fully elucidated. Oztürk and colleagues reported the administration of 50 mg of sildenafil 1 hour before performing flowmetry produced a small but statistically significant increase in the maximum urinary flow in 102 men with ED with and without LUTS/BPH [Oztürk *et al.* 2012]. However, this finding was not confirmed in studies with tadalafil [Roehrborn *et al.* 2010; Gacci *et al.* 2012].

The urinary symptoms caused by BPH have been classically treated with alpha-adrenergic blockers with marked improvement. Oelke and colleagues showed that tadalafil is not inferior to the

alpha-adrenergic blocker tamsulosin in terms of improving LUTS/BPH [Oelke *et al.* 2012].

In the already mentioned study by Gur and colleagues, the authors assessed the impact of partial vesical obstruction on erectile function of rats and one group was treated with alfuzosin, an alpha-adrenergic blocker agent [Gur *et al.* 2008]. The authors verified that functional (diminished contractions in cavernous body muscle fibers, induced by acetylcholine and electrical stimulus) and molecular changes (alteration in expression and bioavailability of nitric oxide) were partially reverted by treating with an alpha-adrenergic blocker. More recently, the same group [Gur *et al.* 2012] demonstrated alpha-adrenergic blockage produces relaxation of the muscle fibers of human cavernous body that is comparable to PDE-5i. Furthermore, in the past it was shown that the intracavernous and oral use of phentolamine and phenoxybenzamine caused erection in men with erectile dysfunction [Padma-Nathan *et al.* 2002; Glina *et al.* 2008].

In the already cited study by Oger and colleagues, the authors assessed the effect of sildenafil and doxazosin in the smooth muscle fibers isolated from human prostate and cavernous body, and reported both drugs had a relaxing effect, reducing adrenergic tonus, on both tissues [Oger *et al.* 2009]. The combination sildenafil–doxazosin presented a statistically superior effect compared with isolated compounds. Similar results were obtained with the association of tadalafil and alfuzosin [Oger *et al.* 2010].

From the clinical point of view, Van Moorselaar and colleagues used alfuzosin 10 mg, daily, to treat LUTS/BPH in 3076 men (mean age of 65.9 years) during 1 year [Van Moorselaar *et al.* 2005]. In this population, 2434 males were sexually active in the beginning of the study, and according to the Danish Prostate Symptom Score (DAN-PSSsex), 65.3% complained of ED, which they strongly related to severity of LUTS/BPH and poor quality of life. At the end of treatment the authors noted that in addition to significant improvement in the IPSS and in quality of life, the patients reported marked improvement in erection rigidity. Demir and colleagues treated men with LUTS/BPH with doxazosin 4 mg, for 6 months [Demir *et al.* 2009]. After this period they observed a significant improvement in urinary symptoms and better IIEF in patients who complained of ED at baseline. With the same

purpose, Jung and colleagues treated 304 patients with LUTS/BPH and ED for 3 months with 0.2 mg of tamsulosin per day [Jung *et al.* 2009]. Three months later improved urinary symptoms correlated with significant improvement in the IIEF-5 and its domains. Although the studies are not placebo-controlled and randomized, these data showed that managing urinary symptoms seems to have an impact on erectile function. Jeug and colleagues stated that objective improvement in urinary flow was associated with marked improvement in the IIEF-5 [Jeug *et al.* 2009].

Likewise, in a study with a small sample, but that was very challenging, Lombardi and colleagues studied a group of 22 men submitted to implant for sacral nerve modulation to treat LUTS, who presented with ED as per the IIEF-5 [Lombardi *et al.* 2008]. The authors noted that after a mean follow up of 29 months, seven individuals, particularly those presenting disorder of neurogenic origin had a significant improvement of erectile function, and the mean IIEF-5 changed from 14.5 at baseline to 22.2 in the final visit. This study is one of those confirming that improved LUTS may have a positive impact on erectile function, although one can speculate that sacral nerve modulation can cause a beneficial effect on isolated cavernous innervation.

Discussion

ED and LUTS/BPH are clinical situations that simultaneously occur in a considerable number of men [Seftel *et al.* 2013]. The epidemiological studies clearly demonstrated that voiding dysfunction is a risk factor for developing ED [Laumann *et al.* 1999; Braun *et al.* 2000; Morillo *et al.* 2002]. This correlation is not certainly valid for all cases of ED, as not all patients with ED suffer from other comorbidities such as diabetes or depression.

Nonetheless the experimental models showed that, at least in rats and rabbits, making a partial obstruction to urinary flow triggers voiding disorder as well as ED [Chang *et al.* 2005; Gur *et al.* 2008; Kobayashi *et al.* 2011; Lin *et al.* 2012]. Apparently there are two ways to justify this fact: increased expression and activity of Rho-kinase [Chang *et al.* 2005] or altered expression and bioavailability of nitric oxide [Gur *et al.* 2008] or of nitric oxide synthase [Kobayashi *et al.* 2011] in the smooth muscles of cavernous body. Increased adrenergic tonus also leads to enhanced expression of Rho-kinase pathway

interfering with voiding and erectile functions [Oudot *et al.* 2012]. Although those data came from animal models, one can assume that partial obstruction elicits structural and functional changes which could explain the symptoms in humans. The weaker hypothesis, with less confirming data, relates arteriosclerosis leading to pelvic arterial insufficiency and, consequently, to ED and LUTS/BPH. However, El Sakka showed a correlation between Doppler ultrasound findings of cavernous arterial insufficiency and LUTS [El Sakka, 2005].

The presence of PDE-5 in the lower urinary tract of rats [Tinel *et al.* 2006], the action of PDE-5i in the prostate muscles [Oger *et al.* 2009, 2010; Angulo *et al.* 2012] and clinical improvement of patients with LUTS/BPH using these drugs, which traditionally enable erection [Gacci *et al.* 2012], demonstrated that, at least from a therapeutic point of view, ED and LUTS/BPH can be treated in the same manner.

It is worthwhile mentioning that even the alpha-adrenergic blockers, one of the main drugs to treat LUTS/BPH, facilitate relaxation of isolated fibers of smooth cavernous muscles [Gur *et al.* 2008, 2012]; in addition these agents can revert functional and molecular alterations triggered by partial vesical obstruction [Gur *et al.* 2008].

The association of LUTS/BPH and ED does not explain all cases of patients with voiding and erectile disorders, but the data indicate that at least part of the voiding alterations can lead to ED, and are undoubtedly a risk factor.

However, due to lack of data, it is not clear whether the opposite situation is true, that is, would ED be a risk factor for LUTS/BPH? Would the presence of some forms of ED make men develop voiding disorders? Further experimental and clinical studies are required to find negative or positive answers.

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Conflict of interest statement

Sidney Glina is speaker, investigator and member of Advisory Board of Lilly Brazil; speaker and investigator for Pfizer Brazil and speaker for Bayer Healthcare Brazil. There is no conflict of interest for Felipe P. A. Glina.

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