New Findings in Benign Prostatic Hyperplasia and Incontinence

Highlights From the 26th Annual Congress of the European Association of Urology, March 18-22, 2011, Vienna, Austria

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The 2011 annual congress of the European Association of Urology (EAU) took place in Vienna from March 18 to 22. Delegates from over 100 countries gathered to share new insights and learn about new advances in the field of urology and all its subspecialties. Unfortunately, the massive earthquake and nuclear accident in Japan prevented a number of Japanese urologists from attending the congress due to travel obstacles. In this review, we highlight some of the findings and the clinical significance of several of this year's important abstracts concerning benign prostatic hyperplasia (BPH) and incontinence.

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Benign Prostatic Hyperplasia

Assessment

Van Doorn and colleagues[1] presented the results of the Krimpen study, a longitudinal population-based study that evaluated the prevalence and incidence of nocturia and the association between nocturia and death in older men. Nocturia was defined as two or more voids per night based on the International Prostate Symptom Score (IPSS) nocturia question. A total of 1688 men, aged 50 to 78 years, without any history of prostate or bladder cancer and no history of transurethral surgery were included. Nocturia was assessed at baseline and after 2.1, 4.2, and 6.5 years. A significant increase in the prevalence of nocturia could be observed for the total group after 6.5 years ($P < .001$; from 25.0% to 34.1%). Incidence was highest in the group aged 65 to 69 years and lowest in the youngest age group (those aged 50 to 54 years). In contrast, resolvance rates were lowest in the oldest age group and highest in the group aged 55 to 59 years. Data for 89% (1498 of the 1688 men) were eligible for mortality analysis. Adjusted for age and after correction for other cofounders, no association between nocturia and death could be observed (relative risk, 1.31; 0.98-1.75; $P = .66$). In conclusion, the prevalence of nocturia is high, but also highly fluctuant. Therefore, calculation of valid incidence rates and the evaluation of the association of nocturia and mortality risk remain complex tasks.

When BPH is causing lower urinary tract symptoms (LUTS), a variety of treatment options including changes

in lifestyle, medical treatment, and surgery, are available. In their prospective study Graham and associates[2] enrolled 178 consecutive patients with LUTS secondary to BPH to identify predictors for failure of medical treatment. Medical treatment included lifestyle modification advice, adjustment of fluid intake, pelvic floor exercises, α-blockers, anticholinergics, and 5α-reductase inhibitors (5ARIs). Medical treatment failure was defined as necessity for transurethral resection of the prostate (TURP). Assessment of LUTS was performed using the American Urological Association (AUA) symptom score, bother score, and quality of life score (QoL). Furthermore, transrectal ultrasound (TRUS) was performed to measure prostate size at baseline. After a 17-year follow-up, 50 patients (28%) underwent TURP, with over two-thirds (36 patients) being treated surgically within the first 3 years. Patients who failed medical treatment had significantly higher AUA symptom and bother scores at baseline. However, prostate size was not found to predict failure of medical treatment in patients with LUTS secondary to BPH.

Lee and associates[3] reported on the results of the Hallym aging study, which is a population-based cohort study that investigated the relationship between LUTS and depression. A total of 382 men aged over 45 years were included. LUTS and depression were assessed via IPSS and the Geriatric Depression Scale, respectively. Approximately 206 men (53.9%) had moderate to severe LUTS (IPSS $>$ 7) and 199 (52.1%) had depression. Results showed that patients with moderate to severe depression were two to three times more likely to have moderate to severe LUTS than men without depression (moderate, odds ratio [OR] = 2.21, confidence interval [CI], 1.21-4.03, P = .010; severe, OR = 2.70, CI, 1.21-6.07, P = .016). Additionally, patients with moderate/severe LUTS were three to five times more likely to have depression than men with no or mild LUTS. However, it remains unclear whether these results are based on unidirectional or bidirectional causality. Nevertheless, depression is something that should be addressed by urologists when treating patients with LUTS.

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Medical Therapy

Erectile dysfunction (ED) and LUTS secondary to BPH frequently go hand in hand in the aging male population. Roehrborn and coauthors[4] presented data on the impact of tadalafil on BPH-LUTS and erectile function (EF) scores in sexually active men aged ≥ 45 years with BPH-LUTS for $>$ 6 months and ED for ≥ 3 months. A total of 606 men were randomized in this phase III study to receive tadalafil, 2.5 mg (n = 198), or tadalafil, 5 mg (n = 208), or placebo (n = 200). Results showed significant improvements in International Index of Erectile Function (IIEF)–EF domain scores in both tadalafil groups as compared with placebo (least squares mean change: placebo, 1.8; tadalafil, 2.5 mg, 5.2; tadalafil, 5 mg, 6.5; both $P <$ .001). Patients treated with tadalafil, 5 mg, showed significant improvement in total IPSS, whereas no significant improvement was seen in the placebo and the tadalafil groups (tadalafil, 5 mg, −6.1, $P <$ .001; placebo, −3.8; tadalafil, 2.5, mg, −4.6, P = .18). Once-daily 5-mg tadalafil for 12 weeks resulted in statistically significant improvements in IIEF-EF and total IPSS, hence, demonstrated efficacy in the treatment of men with both BPH-LUTS and ED.

The reduction in volume of the prostate and the decrease of urethral obstruction are key principles in the management of BPH with 5ARIs. ED, decreased libido, and decreased ejaculate volume are common side effects seen in patients treated with these agents. Zhao and colleagues[5] investigated the potential role of 5ARIs in the induction of fibrosis of the prostate via western blotting and enzyme-linked immunosorbent assay in resected prostatic tissue. A total of 20 patients, who underwent TURP for moderate-to-severe LUTS, were included in the study. Ten patients received α-blockers alone and 10 patients received 5ARIs plus α-blockers, for at least 1 year prior to surgery. Results showed that three isoforms of nitric oxide synthase (NOS) were overexpressed in the 5ARI group and the expression of transforming growth factor (TGF)-β1, TGF-β2, and *p*-smad2/3 increased about two-fold

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as compared with the control group. In conclusion, the group demonstrated that the NOS overexpression may be of importance in smooth muscle relaxation and therefore improvement of symptoms. However, patients treated with 5ARI may be at higher risk of fibrosis of the prostate due to excessive TGF-β signaling.

Resection for BPH

An interesting contribution concerning safety in the operating room was made by Undre and colleagues.[6] In their study, 20 cases in a urology operating room were observed in real time by a psychologist and a surgeon. A validated tool was used by the psychologist to assess interruptions in type (related to communication, equipment, and others) and severity (on a 1 to 9 scale). The task checklist of the Observational Teamwork Assessment for Surgery tool was used by the surgeon to assess safety. A total of 137 interruptions were observed during the cases (85 communication related and 52 others). The operating room teams were affected by a median of six interruptions per hour (range, 2-14). Results showed that communication interruptions generated by surgeons and external visitors were most disruptive. Also, more frequent intraoperative interruptions were associated with lower safety task completion rates.

Since its first use in 1993, transurethral needle ablation (TUNA) of the prostate has become increasingly popular as a minimally invasive treatment option for patients with BPH. Tubaro and colleagues[7] presented results of the EAU Real-Life Data Registry on TUNA of the prostate. Patient data from 20 centers in nine European countries were uploaded by the investigators via an internet-based data collection and analysis tool (enCapture™ Advanced Patient Management System). A total of 526 patients were included: 13% had a history of acute urinary retention (AUR), 64% had prior medical treatment, and 2.7% had prior minimally invasive treatment of BPH. Mean duration of the procedure was 31 minutes and 99% of the patients were satisfied or very satisfied with the comfort during TUNA. In 25% (132) of patients, therapy failure occurred, with 92 requiring medical treatment and 33 requiring TURP. However, when baseline was compared with the endpoint (mean follow-up of 34.8 months after TUNA), significant improvements in total IPSS, IPSS-QoL, and maximum flow rate (Q_{max}) for up to 4 years could be observed.

Placer and colleagues[8] prospectively evaluated the role of Holmium laser enucleation of the prostate (HoLEP) on sexual function in men with LUTS secondary to BPH. A total of 100 consecutive patients were enrolled, and four questionnaires were used to assess LUTS, EF, and QoL: IIEF-5, International Consultation on Incontinence Questionnaire-Male Sexual Matters associated with Lower Urinary Tract Symptoms, AUA-SS questionnaire, and QoL index of the intraclass correlation coefficient. Total, free, and bioavailable serum testosterone levels were determined in 50 patients. All patients were evaluated prior to HoLEP, and at 3 months and 12 months following surgery. Results showed significant improvements in the questionnaires assessing urinary symptoms and the impact of these symptoms in QoL (AUA-SS and QoL). The number of patients suffering from ED did not differ significantly before and after HoLEP. A sharp increase was observed in the percentage of patients (from 33% to 80%) with absent or severely decreased ejaculation after surgery. However, retrograde ejaculation was not interpreted as a problem by most patients. In conclusion, HoLEP does not seem to affect EF and serum testosterone levels.

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Another interesting contribution with regard to HoLEP was made by Schoensee and colleagues.[9] The group retrospectively evaluated 630 patients who underwent HoLEP for either BPH or prostate cancer prior to curative external beam radiation. Complete data including age, prostate-specific antigen, TRUS-derived prostate volume, maximum flow (Q_{max}), residual urine, IPSS, pre-existing incontinence, surgical volume, and net laser time were available in 317 patients in the final analysis. A total of 28 men (8.8%) were incontinent prior to surgery using 1 to 10 pads per day. Postoperative dripping was seen in 27 patients (8.5%), urgency symptoms in 52 patients (16.4%), and 47 patients (14.9%) required anticholinergic agents after surgery. Risk factors for urge incontinence were low: preoperative residual urine ($P = .04$) and need for postoperative anticholinergic medication ($P < .001$). Risk factors for stress urinary incontinence (SUI) were long laser time ($P = .035$) and the presence of incontinence at discharge ($P < .001$). This report clearly shows that careful patient selection is necessary and up to 20% of men may be affected by incontinence after HoLEP.

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Incontinence

Overactive Bladder (OAB) and Detrusor Overactivity

Wagg and colleagues[10] presented results of their placebo-controlled, multicenter study observing the efficacy, tolerability, and patient-reported outcomes (PROs) in 794 older patients treated with fesoterodine (FESO) for OAB symptoms. At baseline, patients experienced symptoms for at least ≥ 3 months, with a mean of ≥ 8 micturitions and ≥ 3 urgency episodes/24 h. After randomization to double-blind treatment with FESO, 4 mg (elevated to 8 mg), or placebo for 12 weeks, the authors demonstrated a significant improvement in diary and PRO measures with significantly greater PRO response rates with FESO compared with placebo. Under treatment with FESO, mean reduction in urgency was greater for patients aged ≤ 75 years and aged > 75 years, as well as for morning and evening dosing. Similar results were reported for the Treatment Benefit Scale response rates. Dry mouth and constipation were the most frequent adverse events (AEs) with rates of 34% and 9% in the FESO group and 8% and 3% under the placebo treatment, respectively, showing discontinuation rates due to dry mouth, urinary retention, or dysuria in 14% and 5%, respectively. In conclusion, fesoterodine is well tolerated by older patients with OAB symptoms and showed significant improvements in diary variables and patient-reported outcome.

The selective β3-adrenoreceptor agonist mirabegron in the treatment of OAB symptoms was observed in a phase III study by Khullar and colleagues.[11] With similar inclusion criteria as the previous study, the group enrolled adult patients with OAB symptoms for their multi-institutional, single-blind, placebo-controlled trial. Patients received either placebo or mirabegron, 50 or 100 mg, or tolterodine (slow release), 4 mg, once daily for 12 weeks. Change from baseline to final visit regarding mean number of incontinence episodes/24 h and micturitions/24 h were chosen as coprimary endpoints of the study. Upon final analysis, patients under mirabegron treatment (both dosages) showed statistically significant improvements regarding the efficacy variables. Hypertension, dry mouth, and headache were the most commonly reported AEs in all groups. As with fesoterodine, mirabegron can be seen as a well-tolerated and efficient treatment option in patients with OAB symptoms.

Another very interesting contribution was made by Coehlo and associates[12] regarding the treatment with onabotulinum A (OnabotA) for patients with OAB symptoms. The group observed the diffusion patterns of OnabotA, measured by the Synaptosomal-Associated Protein-25 (SNAP-25), being a reliable marker of the neurotoxin dispersion. Male adult Dunkin-Hartley guinea pigs either underwent a single dorsal intramural injection of 2U OnabotA diluted in 2 or 20 μl of saline or 10 injections of 5U diluted in 200 μl of saline. Animals injected with normal saline were used as controls and the synaptic fusion complex SNAP-25c was evaluated using immunohistochemistry. It was reported that a single injection spreads the activity of the neurotoxin until the opposite site of the guinea pig bladder, especially when higher saline volumes were used to dissolve the agent. The injected volume seems to be important in the spread and action of OnabotA, which therefore, should be considered when administering the agent in patients with OAB.

Regarding the use of sacral neurostimulation in neurogenic detrusor overactivity, Monga and Linsenmeyer[13] prospectively assessed a new transdermal amplitude-modulated signal (TAMS). Their single-blind, randomized, crossover study included 20 patients suffering from symptoms after spinal cord injury or from multiple sclerosis. After initial and continuous cystometrogram recording and stimulation with a 5 Hz or 10 Hz signal, the patients underwent posttreatment evaluation including visible analogue scales (VAS). A significant increase in bladder capacity was demonstrated ($P = .0003$) for the 5-Hz signal for all subjects, especially in patients appropriate to the American Spinal Injury Association Impairment Scale (AIS) group A. The authors reported higher incidence of motor response than the control signal, with minimal pain and discomfort throughout the study. These early results demonstrate the feasibility of the novel TAMS treatment of symptoms of neurogenic detrusor overactivity, especially in AIS group A patients.

Surgical Treatment of Incontinence

The Russian group of Kasyan and Pushkar[14] reported on their long-term results with the transobturator tension-free tape in the treatment of mixed urinary incontinence (MUI) in female patients. All patients underwent the transobturator tension-free tape (TVT-O) procedure and were postoperatively examined with consequent cough stress test, uroflowmetry, and postvoid residual urine. VAS served as the assessment tool of choice. Out of 276 patients treated with the midurethral synthetic tape, 211 patients suffered from postoperative pure SUI (group 1) and 65 from MUI with stress symptoms (group 2). No statistically significant differences were reported in objective and subjective cure rates on short-term ($P = .098$-0.690) and long-term ($P = .258$-0.845) follow-up of both groups. In this study, objective and subjective

cure rates of patients with MUI can be compared with the pure SUI group, 86.2% and 87.7% in group 2, respectively. Therefore, it can be stated that MUI with predominance of the stress component may be successfully treated with the TVT-O procedure.

Postprostatectomy incontinence (PPI) remains a common problem after radical surgery for prostate cancer. In a study by Comiter and associates[15] from three US centers, it was demonstrated that the new quadratic Virtue® sling (Coloplast USA, Minneapolis, MN) shows good results compared with common pure prepubic (PP) and transobturator slings. The main point of interest in this study was the resistance of the sling to leakage, measured by the retrograde leak point pressure (RLPP) during different intraoperative key fixation steps. A total of 16 consecutive men with PPI underwent the Virtue sling technique and their RLPP was evaluated by perfusion sphincterometry at baseline and during surgery. After a baseline value of 26.4 ± 9.1 cm, the step of TO fixation let the mean RLPP increase to 45.9 ± 7.0 cm water. After the next surgical step (PP tensioning), the mean RLPP increased to 59.9 ± 12.1 cm and finally to 68.4 ± 6.4 cm water after the final PP fixation step. The authors concluded that different components of the quadratic fixation of the Virtue sling are contributing to the increasing urethral resistance. Generally, this new quadratic fixation technique appears to have a greater ability to provide urethral compression.

Finally, we would like to discuss the study by Chartier-Kastler and colleagues,[16] who evaluated the impact of urisheaths (type: Conveen® Optima; Coloplast USA) versus absorbent products (diapers) on QoL. This randomized, controlled, crossover, multicenter trial included 61 male patients with stable, moderate, or heavy urinary incontinence. Both leakage diaries and different types of questionnaires were used to assess the current QoL of the patients enrolled. Results demonstrated that questionnaires were scored lower with urisheaths and indicated an improvement in QoL for "limitations of daily activities" ($P = .01$) and "impact of incontinence" ($P < .05$). Approximately 69% of the patients preferred urisheaths, which were also scored significantly higher for efficacy, self-image, odor management, discretion, and skin integrity. Therefore, urisheaths seem to have a positive impact on the QoL and may be recommended in preference to absorbent products in incontinent male patients. ■

[Reviewed by Alex Farr, MD, Sabina Sevcenco, MD, and Bob Djavan, MD, PhD]

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Main Points

- Results of the Krimpen study showed that the prevalence of nocturia is high, but also highly fluctuant.
- Patients with higher American Urological Association symptom and bother scores are more likely to fail medical treatment of benign prostatic hyperplasia (BPH).
- Once-daily tadalafil, 5 mg, for 12 weeks demonstrated efficacy in patients with both erectile dysfunction and lower urinary tract symptoms (LUTS)/BPH.
- The majority of patients treated with transurethral needle ablation showed clinical benefit that was maintained for almost 3 years.
- Holmium laser enucleation of the prostate does not seem to affect sexual function, but patients should be carefully selected for this procedure.
- Fesoterodine and mirabegron are well-tolerated, safe, and efficient agents in patients with overactive bladder symptoms.
- The injected volume of onabotulinum A seems to be important in spread and action, and should be considered.
- In neurogenic detrusor overactivity, the new transdermal amplitude-modulated signal is a feasible option, especially for American Spinal Association Impairment Scale 'group A' patients.
- In women, mixed urinary incontinence with stress symptoms can be treated with the transobturator tension-free tape procedure.
- The new quadratic fixation Virtue® (Coloplast USA, Minneapolis, MN) technique shows good results in postprostatectomy patients.
- Urisheaths have a positive impact on quality of life and may be recommended in preference to absorbent products in incontinent men.

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