Progression of LUTS/BPH
: Focus on Bladder

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Introduction

• LUTS/BPH is highly prevalent and have a negative impact on QoL
• LUTS/BPH may actually be due to three components
Introduction

• LUTS/BPH is a slowly but chronically progressive disease

• Role of alterations in bladder structure and function as a risk factor for the progression of LUTS/BPH
Factors affecting bladder structure & function

- Local factors
- Hormonal changes
- Bladder outlet obstruction
- Aging
- Ischemia
- High nocturnal diuresis
- Concomitant diseases
- Neurologic diseases
BPH progression and its assessment

- Worsening of lower urinary tract symptoms
- Occurrence of LUTS/BPH complications
  - Occurrence of AUR
  - Increased risk of needing surgery
  - Urinary tract infection
  - Renal insufficiency
- Deterioration in urinary flow rate
- Increase in prostate volume
- PSA
Most LUTS/BPH Progression Events Were Due to Symptom Progression

Distribution of BPH progression events

- AUR: 12%
- Incontinence: 9%
- UTI/urosepsis: 1%
- Renal insufficiency: 0%
- >4-point AUA-SI increase: 78%

MTOPS (Medical Therapy Of Prostatic Symptoms)
Symptoms Related to Male Lower Urinary Tract Dysfunction

LUTS/BPH

No BOO

OAB Sx: Frequency, Urgency, and/or Urge Incontinence

Bladder dysfunction

Storage Irritative

Benign Prostatic Obstruction (BPO)

Voiding Obstructive

Voiding Sx: Hesitancy, Weak Stream, Straining, Dribbling
Role of bladder for LUTS/BPH progression (voiding sx)

Initial period of obstruction

Compensated stage

Decompensated stage

Emptying failure

Kirby et al, 1996
Impaired emptying after BPO

- Increasing amounts of extracellular matrix (ECM) components such as collagen are deposited in the bladder, leading to impaired emptying.
- Alteration of ECM expression is thought to be a pathophysiological feature in long-term obstruction.

*Kim et al, Neurourol Urodyn, 2000*
Role of bladder for LUTS/BPH progression (storage sx)

- Partial denervation
- Ischemia
- Detrusor Muscle
- Expression of NGF

- Supersensitivity to Ach
- Reduced response to intramural nerve stimulation
- Increased EC btw cells
- Hypertrophy/hyperplasia
- Instability of membrane potential
- Altered IC Ca++ regulation
- Hypertrophy of afferent and efferent neurons

- Reorganization of spinal mict. Reflex (C-fiber med.)
- Altered Na+ channel expression
Pathophysiology of OAB in LUTS/BPH

Marked changes in bladder

- Neuroplasticity and changes in the afferent input
- Plasticity of urothelial signaling
- Changes in intercellular communication
Pathophysiology of OAB in LUTS/BPH

- Neuroplasticity (Afferent plasticity)

  - Recruitment of lower threshold, spontaneous firing afferent
  - Increase of NGF content

  Irritated, obstructed Bladder

  Parasympathetic Postganglionic Neuron

  Dorsal Horn Interneuron

  Preganglionic Neuron

  Sacral Spinal Cord

  Enhanced synaptic transmission
Pathophysiology of OAB in LUTS/BPH

• Plasticity of urothelium

Andersson, Urology, 2002
Pathophysiology of OAB in LUTS/BPH

- Changes in intercellular communication:
  increased expression of connexins in LUTS/BPH patients with OAB

$\text{GAPDH} \rightarrow$  
$\text{Cx26} \rightarrow$  
$\text{DO}(+) \text{ DO}(-)$

$\text{GAPDH} \rightarrow$  
$\text{Cx43} \rightarrow$  
$\text{DO}(+) \text{ DO}(-)$

*Kim et al, ICS, 2004*
Urothelium

Chemical transmitters

Sensory nerve

Interstitial cell (myofibroblast)

Electrical communication

Spinal cord

Smooth muscle
LUTS/BPH with Coexisting OAB

• The prevalence of BOO combined with OB was 45% and “pure” BOO was 55% of the total cohort

• The patients with BOO and OAB: older, higher PSA, smaller voided volumes, more obstructed
With increasing obstruction grade & age, the rate of DO increased

Choi & Lee, Korean J Urol, 2005
Storage score is useful parameters to the patient’s risk for progression

- Among men with LUTS/BPH and no history of AUR, the overall symptoms score and storage subscore are useful parameters in identifying patients at risk for future surgery

(A): entire cohort of placebo-treated patients
(B): patients without a preceding episode of AUR

Roehrborn et al, Eur Urol, 2002
Changes in symptom and bother between baseline and 3 years

Lee et al, Eur Urol, 1996
Role of the bladder in LUTS/BPH progression

- BOO
- "Detrusor hypertrophy"
  - Detrusor underactivity
  - Detrusor overactivity

Progression of LUTS/BPH
Changes in bladder mass

Malkowicz et al, J Urol, 1986

Uvelius et al, J Urol, 1984
Detrusor hypertrophy leads to an increase in BWT

• BWT distribution in 100 BPH patients

\[ p < 0.0001 \text{ for Kruskal-Wallis 1-Way Anova} \]

*Manieri et al, J Urol, 1998*
The relationship between bladder wall hypertrophy and function

<table>
<thead>
<tr>
<th></th>
<th>Qmax</th>
<th>PdetOp</th>
<th>PdetQmax</th>
<th>Pvoidmin</th>
<th>URA</th>
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<tbody>
<tr>
<td><strong>BWT</strong></td>
<td>r = 0.47</td>
<td>r = 0.62</td>
<td>r = 0.82</td>
<td>r = 0.75</td>
<td>r = 0.58</td>
</tr>
<tr>
<td><strong>p&lt;</strong></td>
<td>0.044</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.007</td>
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</tbody>
</table>

BWT: bladder wall thickness

- Relationships between morphologic changes and bladder function are of clinical importance

The effect of $\alpha$-blocker on prevention of bladder wall hypertrophy

- Animal studies

Effect of doxazosin on blood flow

Effect of doxazosin on bladder weight

Das et al, Neurourol Urodyn, 2002
**Effect of $\alpha$-blocker on ultrasound estimates of bladder weight**

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
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<tbody>
<tr>
<td></td>
<td>Tamsulosin (N=16)</td>
<td>Tamsulosin (N=18)</td>
<td>Placebo (N= 36)</td>
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<tr>
<td>Mean baseline</td>
<td>64.1 ±16.2</td>
<td>46.3 ±13.4</td>
<td>48.4 ±11.0</td>
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<tr>
<td>Mean at 12 weeks</td>
<td>55.5 ±12.7</td>
<td>38.3 ±13.2</td>
<td>44.3</td>
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<tr>
<td>Mean change at 12 weeks</td>
<td>-8.6 ±6.2</td>
<td>-8.0</td>
<td>-4.1 ±13.3</td>
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<tr>
<td>% change at 12 weeks</td>
<td>-13%</td>
<td>-17%</td>
<td>-8%</td>
</tr>
</tbody>
</table>

* $p = 0.281$ vs. placebo.

*Sironi D, et al, Arch Ital Urol Androl, 2002*
*Tubaro A, et al, Eur Urol (Suppl), 2003*
Effects of α-blocker on bladder mass and disease progression

• The combined evidence from animal and patient studies suggests a protective effect of α1-AR antagonists on bladder function

• It remains to be seen in adequately powered controlled trials whether α1-AR antagonists can indeed reduce bladder mass and prevent disease progression
Role of the bladder in LUTS/BPH progression

- BOO
  - Detrusor hypertrophy
    - Detrusor underactivity
      - Increased residual urine
        - UTI
        - Bladder stone
    - Detrusor overactivity
      - Acute urinary retention
      - Chronic urinary retention
      - Surgery
      - Chronic renal failure
Conclusions

- The risk factors for LUTS/BPH progression depend on how progression is defined.

- Several studies have shown that most progressed by worsening of symptoms including OAB.

- The structural and functional changes of bladder have a role in progression of LUTS/BPH.
Conclusions

- The changes of the bladder in LUTS/BPH may increase the risk of developing serious complications.

- Treatment of LUTS/BPH should be targeted to the bladder as well as prostate.