Male LUT/BPH

Current Issues and Unmet Needs

What do we know, what don’t we know?
What do we need to know?

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• **What We Know?**
  - Phenotypes – some
  - Risk factors - some
  - Co-mordibilities: ED/ EjD

• **What We Don’t Know?**
  - Who is bothered/who copes?
  - Etiology of symptoms
  - Why variable growth/progression?
  - Genetic influence
  - CNS influences: Disordered sleep, nocturia

**What We Need to Know?**
  - Who will Progress (LUTS)?
  - AUR-CUR/Upper tract?
How to Help men with LUTS Help themselves? (H3 Men)

• To review the evidence on various factors impacting LUTS in men
• To discuss the knowledge base for self-management of LUTS in men
• To identify potential intervention strategies to reduce the impact of LUTS on QoL of men

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
Natcher Conference Center, National Institutes of Health (NIH)
Bethesda, MD
September 21–22, 2016
• What We Know?
  - Phenotypes – some
  - Risk factors
  - Co-morbidities: ED/ EjD

• What We Don’t Know?
  - Who is bothered/who copes?
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  - Genetic influence
  - Disordered sleep vs nocturia vs CNS influences

• What We Need to Know?
  - Who will Progress (LUTS)?
    - AUR - CUR/Upper tract?
The Clinical Phenotype PROBLEM – AGE?

Kaplan-Meier cumulative probability of any treatment

Cumulative incidence of “BPH” treatment (A) and TURP(B) stratified by age at study entry.
The Clinical Phenotype PROBLEM

Prostate Size and proxies?


<table>
<thead>
<tr>
<th>BASELINE</th>
<th>Unadjusted Clinic Cohort</th>
<th>Adjusted</th>
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<tbody>
<tr>
<td></td>
<td>RR 95% CI</td>
<td>RR 95% CI</td>
</tr>
<tr>
<td>TPV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30ml</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>&gt;30 ml</td>
<td>4.2  2.2-82 2.3 1.1-4.7</td>
<td></td>
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<tr>
<td>PSA</td>
<td></td>
<td></td>
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<tr>
<td>&lt;1.4</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;1.4</td>
<td>4.0  2.2-7.3 2.1 1.1-4.2</td>
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Association between baseline measures of LUT dysfunction and risk of any treatment during followup
The Clinical Phenotype PROBLEM

Prostate Size and proxies?

Roerhrborn et al Urology 1999

Four-year incidences of either AUR or BPH-related surgery in those treated with PL or 5ARI.

PSA and prostate volume are predictors of the risk of AUR and the need for surgery.

Baseline values are useful tools in predicting the risk of BPH-related outcomes and choice of therapy.

Arrows denote reduction in risk by the log-rank test.
There is an association between baseline measures and risk of treatment.

In RCT such quantitative variables (baseline IPSS and Qmax) behave paradoxically.
Why? Strict inclusion criteria, resulting regression to the mean, and 'ceiling' effects?
## Risk Factors for LUTS/BPH

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Effect on BPH</th>
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<tbody>
<tr>
<td>Male gender and aging(^1,^2)</td>
<td>Increases risk</td>
</tr>
<tr>
<td>Positive family history(^2)</td>
<td>Increases risk</td>
</tr>
<tr>
<td>Smoking(^2)</td>
<td>Indeterminate effect</td>
</tr>
<tr>
<td>Obesity(^2)</td>
<td>Increases risk</td>
</tr>
<tr>
<td>High physical activity(^1)</td>
<td>Protective effect</td>
</tr>
<tr>
<td>Sexual activity(^1,^2)</td>
<td>Indeterminate effect</td>
</tr>
<tr>
<td>Alcohol(^2)</td>
<td>Protective effect</td>
</tr>
<tr>
<td>Heart disease(^1)</td>
<td>Increases risk</td>
</tr>
</tbody>
</table>

C-Reactive Protein (CRP) Level Correlates with Level of LUTS in BACH Survey

N= 3,757 (1,898 men, 1,854 women)
- Significant association between CRP and LUTS among both sexes.
- Nocturia and straining: men
- Incomplete emptying and weak stream: women.
- The dose-response relationship between increased CRP

Kupelian et al. J Urol
Acute baseline inflammation was unrelated to IPSS at any time.
Chronic baseline inflammation was associated with higher IPSS at baseline, which remained relatively stable throughout the study interval.

Chronic inflammation was associated with larger prostates at baseline as well as increased prostate volume changes from baseline.
Chronic Prostate Inflammation: Severity and Progression of BPH, LUTS and Risk of AUR
Nickel et al, J Urol 2016

Cumulative incidence of AUR as a function of baseline chronic inflammation
Chronic Inflammation
Severity and Progression: BPH, LUTS and AUR

A leading hypothesis:
Inflammation is involved in the etiology of BPH and promotes BPH progression

Inflammation can lead to the development and progression of BPH through a number of proposed mechanisms.

They include immunological and structural mechanisms or the observed link with metabolic syndrome.
LUTS/BPH and Metabolic Syndrome
Low Grade inflammation

- Central Obesity-BMI
- Insulin Resistance (receptor interference)
- Prostatic epithelial cell proliferation

Hyperinsulinemia

- Increase IGF, IGFBP-3
- Reduced Apoptosis

Increases
- CRP
- IL-6 et al.
- WBC
- AP-1 transcription factors*

BPH
LUTS

AP-1 activating protein-1 transcription factors
Inflammatory / Ischemia Bladder/Prostate Model

- Inflammatory Infiltration Bladder / prostate
- Decreased bladder blood flow
- Chronic bladder ischemia/hypoxia
- Structural changes/fibrosis
- LUTS

Key Components:
- Bladder outlet obstruction
- High intravesical pressure
- Functional changes Noncompliance Hyperactivity Impaired contractility
Atherosclerosis-Induced Chronic Ischemia Causes Bladder and Penile Fibrosis

Azadzoi et al.
Autonomic Hyperactivity and LUTS

- Hyperinsulinemia
- Age
- Physical Inactivity
- Obesity-BMI
- Increased Sympathetic Tone
- BPH Growth
- BPH Voiding Dysfunction
- Erectile Dysfunction?

McVary KT et al., Autonomic Nervous System Overactivity in Men with LUTS Secondary to BPH. Journal of Urology 2005
Sleep disorders as a LUTS risk factor

Improvements in LUTS correlate with changes in sleeping abilities over time in men with BPH/LUTS.

While nocturia is significantly associated with sleep disturbance, other changes in overall LUTS are better predictors of changes in sleep dysfunction over time.
• **What We Don’t Know?**

  - Who is bothered/who copes?
  - Etiology of symptoms
  - Why variable growth/progression?
  - Genetic influence
  - Disordered sleep vs nocturia vs CNS influences
How are physicians suppose to react?
BPH – *Pathophysiology*

**Static constriction**
- Increased prostate size

**Dynamic constriction**
- Increased smooth muscle tone of the prostate
- Primary cause of BPH symptoms
LUTS is common and has a multifactorial etiology

The most important causes of LUTS in patients with bothersome symptoms...

Natural History of BPH: Prostate Volume

- 631 men (40-79yo) from Olmsted County, MN
- Prostate volume during a 7-year period (TRUS)
- Estimated prostate growth rates increased by 1.6% per year across all ages
- Higher baseline prostate volume associated with higher rates of prostate growth
Genetics of LUTS/BPH

• 4-6 X increased age-specific risk of surgery for BPH among all relatives of cases

• Monozygotic twin concordance rates of 26%-63% reported for LUTS/BPH

• Estimate: genetic factors contribute ~72% of the risk of moderate/severe LUTS
Among 38 SNPs associated with CaP risk, several associated with aspects of a well-characterized LUTS phenotype.

- Confirmed a prior association between 5p15 and BPH interventions (Icelandic men)
- SNPs on chromosome Xp11, 9q33, 8q24 and 7q21 may be predict severe LUTS

Can genetic tests predict which men are at greatest risk for severity of LUTS and bother?
Erectile Dysfunction and LUTS Severity

Multinational Survey of the Aging Male-7

- No, I cannot get an erection
- Net reduction of stiffness

<table>
<thead>
<tr>
<th>LUTS Severity</th>
<th>50-59 Years</th>
<th>60-69 Years</th>
<th>70-79 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>2</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Mild</td>
<td>12</td>
<td>41</td>
<td>20</td>
</tr>
<tr>
<td>Moderate</td>
<td>25</td>
<td>50</td>
<td>31</td>
</tr>
<tr>
<td>Severe</td>
<td>45</td>
<td>52</td>
<td>44</td>
</tr>
</tbody>
</table>

Incidence, %

ED increases with LUTS severity

IPSS, International Prostate Symptom Score.

N=12,815 men aged 50-80 years from the US and six European countries.

Symptoms were classified as absent (IPSS=0), mild (IPSS ≤7), moderate (IPSS 8-19), or severe (IPSS ≥20).

LUTS-BPH and ED

Common Pathophysiologic Mechanisms

- Reduced NO–cGMP signaling
- Increased RhoA–ROCK signaling
- Autonomic hyperactivity
- Pelvic atherosclerosis

Functional Consequences at Tissue Level

- Reduced function of nerves and endothelium
- Altered smooth muscle relaxation or contractility
- Arterial insufficiency, reduced blood flow, and hypoxia-related tissue damage

Chronic inflammation  Steroid hormone unbalance

Comorbidities
Hypertension, metabolic syndrome, diabetes, etc.
IPSS Score: Mean Change from Baseline to 12-weeks

- Placebo
- Tadalafil 2.5
- Tadalafil 5.0
- Tadalafil 10.0
- Tadalafil 20

Clinical meaningful improvement

* Tadalafil 2.5mg p<.05 at week 4, 8 and 12, and Tadalafil 5, 10, and 20 mg p<.001 for Weeks 4, 8, and 12 compared to placebo

Compared to placebo (Ancova analysis)
Roehrborn et al J Urol 2008 Oct;180(4):1228-34
Biological Evidence for Causal Relationship Between BPH, LUTS, and ED

- NOS/NO theory
- LUTS and autonomic hyperactivity
  - metabolic syndrome
- Alternate pathway: ET-1/Rho kinase
- Pelvic atherosclerosis
ED-LUTS: NOS/NO Theory

Diabetes
Smoking
Dyslipidemia
Hyperinsulinemia

Reduced NOS/NO

SMC Proliferation
structural changes
bulk changes

SMC Contraction
functional changes
noncompliance
outlet resistance

LUTS
What We Know?

Phenotypes

Risk factors

Co-morbidities: ED/EjD

What We Don't Know?

Who is bothered/who copes?

Etiology of symptoms

Why variable growth/progression?

Genetic influence

Disordered sleep vs nocturia vs CNS influences

What We Need to Know?

Who will Progress (LUTS)?

AUR-CUR/Upper tract?
Comparative Effects of Diet on Ventral Prostate Growth

Standard Chow
“Western diet”: 45% energy as animal fat (lard)
35% as refined carbohydrate
60% lard, 20% refined CHO diet

Marked Influence:
- body weight, ventral prostate and [³H]NE turnover rates

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>Chow (21)</th>
<th>60% lard diet (21)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body wt (g)</td>
<td>358.8 ± 4.1</td>
<td>369.0 ± 4.1</td>
<td>0.0870</td>
</tr>
<tr>
<td>Prostate wt (mg)</td>
<td>498.4 ± 11.2</td>
<td>548.1 ± 14.6</td>
<td>0.0101</td>
</tr>
<tr>
<td>bwt adj’d</td>
<td>500.8</td>
<td>545.8</td>
<td>*</td>
</tr>
<tr>
<td>Prostate NE (ng)</td>
<td>452 ± 14.9</td>
<td>387 ± 13.4</td>
<td>0.0026</td>
</tr>
<tr>
<td>Prostate NETR (ng NE/hr)</td>
<td>19.9 ± 3.3</td>
<td>12.9 ± 2.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>IBAT NETR (ng NE/hr)</td>
<td>59.4 ± 8.0</td>
<td>66.1 ± 14.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Prostate weight was not significantly related to body weight.
Dietary-Not Supplemental - Carotenoids and Vitamin C Associate with Decreased LUTS

• Consuming greater amounts…
  ◆ Lycopene
  ◆ β-carotene
  ◆ Total carotenoid
  ◆ Vitamin A

• Results in ~40-50% decreased odds of LUTS compared with the lowest quartiles
  (β-carotene and storage symptoms, OR = 0.56, 95% CI = 0.39, 0.82; p-trend = 0.02).

• High-dose supplemental vitamin C: increased LUTS (vitamin C ≥ 250 mg/d, OR = 1.83, 95% CI = 1.21, 2.77; p-trend = 0.02)

Results from the BACH Survey: J Nutr. 2010 Dec 22.
Obesity Effects Response to Medical Treatment?

- Obese (>30 BMI) had the greatest improvement in IPSS total and storage and voiding subscores compared with baseline.

- This group also had the largest placebo response among the groups.
Central obesity is predictive of persistent storage LUTS after surgery for BPH: results of a multicenter prospective study

Mean and 95% confidence interval of the mean of postoperative IPSS storage score, stratified according to the number of MetS parameters (age adjusted wald 1.090, p=0.009)
Central obesity is predictive of persistent storage LUTS after surgery for BPH: results of a multicenter prospective study

<table>
<thead>
<tr>
<th></th>
<th>p</th>
<th>OR</th>
<th>LL</th>
<th>UL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated Waist Circ (&gt;102cm/46in)</td>
<td>0.002</td>
<td>0.21</td>
<td>0.08</td>
<td>0.57</td>
</tr>
<tr>
<td>Elevated Systolic BP</td>
<td>0.480</td>
<td>0.70</td>
<td>0.26</td>
<td>1.87</td>
</tr>
<tr>
<td>Elevated GLYCEMIA</td>
<td>0.211</td>
<td>1.95</td>
<td>0.69</td>
<td>5.51</td>
</tr>
<tr>
<td>Elevated TRIGLICERIDE</td>
<td>0.349</td>
<td>1.64</td>
<td>0.53</td>
<td>5.07</td>
</tr>
<tr>
<td>Reduced HDL-CHOL</td>
<td>0.39</td>
<td>0.39</td>
<td>0.11</td>
<td>1.35</td>
</tr>
</tbody>
</table>

5-fold decreased chance of full recovery from TURP than non-central obese males

Odds Ratio (OR) based on full recovery of LUTS (D STORAGE IPSS=100%) vs. partial recovery (D STORAGE IPSS<100%), as derived from a logistic regression mode adjusted for: Age, PSA, prostate volume, smoking, surgical procedure (TURP or OP), presence of MetS.
2 weeks of Pritikin Diet in obese vs. “Trim” cohort (1-28 y)
Impact of Lifestyle: Longitudinal Changes

Incidence of LUTS (AUA-SI >8) in BACH men at follow up as a function of lifestyle factors at baseline
Treatment of LUTS/BPH While Preserving Sexual Function: Randomized Controlled Study of Prostatic Urethral Lift

The Rezūm System

- **IPSS**
  - Baseline: Treatment 22.0, Control 21.9
  - 1 Month: Treatment 14.5, Control 15.1
  - 3 Months: Treatment 10.6, Control 17.5
  - 6 Months: Treatment 9.8, Control 9.8

- **Qmax (ml/sec)**
  - Baseline: Treatment 22.6, Control 21.2
  - 1 Month: Treatment 22.7, Control 21.0
  - 3 Months: Treatment 22.7, Control 22.7
  - 6 Months: Treatment 22.9, Control 22.9

- **IPSS Change from Baseline to 6 Months**
  - Baseline ED Condition (via SHIM)

- **IIEF-EF**
  - Baseline: Treatment 22.6, Control 21.2
  - 3 Months: Treatment 22.7, Control 21.0
  - 6 Months: Treatment 22.7, Control 22.7
  - 12 Months: Treatment 22.9, Control 22.9

- **MSHQ-EjD - Function**
  - Baseline: Treatment 9.3, Control 9.8
  - 3 Months: Treatment 9.7, Control 9.6
  - 6 Months: Treatment 9.7, Control 9.7
  - 12 Months: Treatment 9.3, Control 9.3
**Minimal Clinically Important Difference (MCID)**

- MCID for the EF domain represents the smallest difference in score perceived as a benefit, or clinically meaningful.
- Changes needed: Mild ≥2; Moderate ≥5; Severe ≥7

Control of Sexual Response in Male

Control of Sexual Response in Female