Obesity, Neural Influences, LUTS/BPH and PDE5 Inhibitors

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Obesity Trends* Among U.S. Adults
(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)
LUTS/BPH Epidemiology

Kristal: J Urol- 2007
Examined predictors of LUTS
Age, Baseline LUTS, Hip-waist ratio, ethnicity

Giovannucci et al, 1994 - 25,892 men (HPFU Study)
Abdominal obesity as a risk factor for TURP and LUTS

Meigs (NERI) 2001, Physical activity reduced BPH/LUTS

Glynn: American Journal of Epidemiology - 1985
Examined predictors of BPH
BMI as the only predictor of BPH/TURP
Relationship of Obesity with BPH/LUTS?  
Does waist circumference/waist-to-hip ratio make a difference in surgery risk?

- Increased risk specific to abdominal obesity
- Waist circ. (≥ 102 cm) more likely to have LUTS (OR = 1.48, 95% CI: 0.87, 2.54)

Dahle et al J Urol, 2002

<table>
<thead>
<tr>
<th>Anthropometric Factors</th>
<th>No. Pts./No. Controls</th>
<th>Odds Ratio Adjusted for Age (95% CI)</th>
<th>Odds Ratio Further Adjusted for Education Anthropometric Factors (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body mass index quartile (kg/m²):</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (less than 19.487)</td>
<td>36/67</td>
<td>1 (referent)</td>
<td>1 (referent)</td>
</tr>
<tr>
<td>2 (19.487–21.385)</td>
<td>49/82</td>
<td>1.13 (0.65–1.97)</td>
<td>1.05 (0.60–1.85)</td>
</tr>
<tr>
<td>3 (21.386–23.437)</td>
<td>48/74</td>
<td>1.15 (0.66–2.02)</td>
<td>1.09 (0.61–1.93)</td>
</tr>
<tr>
<td>4 (greater than 23.437)</td>
<td>67/76</td>
<td>1.64 (0.96–2.81)</td>
<td>1.50 (0.86–2.63)</td>
</tr>
<tr>
<td><strong>p Value (test for trend)</strong></td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist-to-hip ratio quartile:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (less than 0.856)</td>
<td>24/74</td>
<td>1 (referent)</td>
<td>1 (referent)</td>
</tr>
<tr>
<td>2 (0.856–0.891)</td>
<td>56/75</td>
<td>2.39 (1.32–4.34)</td>
<td>2.25 (1.23–4.09)</td>
</tr>
<tr>
<td>3 (0.892–0.923)</td>
<td>61/76</td>
<td>2.45 (1.36–4.41)</td>
<td>2.27 (1.25–4.12)</td>
</tr>
<tr>
<td>4 (greater than 0.923)</td>
<td>59/77</td>
<td>2.42 (1.34–4.37)</td>
<td>2.04 (1.10–3.78)</td>
</tr>
<tr>
<td><strong>p Value (test for trend)</strong></td>
<td>0.01</td>
<td></td>
<td>0.06</td>
</tr>
</tbody>
</table>
Association between markers of the metabolic syndrome and LUTS in the NHANES III

*Rohrmann S* et al. *Int J Obes*, 2005

Men (n = 2,372) >60y

- >2 components of the metabolic syndrome: increased odds of LUTS
  
  (OR = 1.80; 95% CI 1.11-2.94)

Noted a strong association with lifestyle linked diseases:

- elevated HgBA1C
- diabetes mellitus
- hypertension
Metabolic Syndrome Correlates with Level of LUTS in BACH Survey

- Prevalence of MetS increases with >AUA-SI (2-7)
- Effect stabilizes with AUA-SI >8
- Overall trend test p-value = 0.003

Kupelian et al. 2009
## Risk Factors for BPH

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

Physical Activity and BPH
Where does this variable epidemiological data leave us?

Bias:
- Case-control studies: clinic/hospitalized
- Largely cross sectional studies

Evolving Treatment:
- Switch from surgery to med Rx

Evolving Definition:
- LUTS, “BPH”, enlargement
Influence of Modifiable Risks on LUTS/BPH

- The relationship between LUTS and objective measures of BPH is lacking

Extrinsic/systemic factors

Anatomic/physiologic derangements

LUTS
LUTS/BPH and Modifiable Risks
Pathophysiologic Mechanisms

- Low grade inflammation
- Hormonal basis
- Sympathetic Hyperactivity
- Direct effect of hyperinsulinemia
- Osmotic diuresis/Glucosuria
LUTS/BPH and Metabolic Syndrome
Low Grade inflammation

Central Obesity-BMI

Insulin Resistance
(receptor interference)

Hyperinsulinemia

Prostatic epithelial cell proliferation

BPH

LUTS

Increase
CRP
IL-6
WBC

Increase IGF

Reduced Apoptosis

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. 2009
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 \([^3\text{H}]\)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>
</tbody>
</table>

IBAT NETR (ng NE/hr)

59.4 ± 8.0

66.1 ± 14.1

\(\text{NS}\)

* Prostate weight was not significantly related to body weight.
Nerve Perturbations
Histological Effects of Denervation

Wang et al 1991

- Reduction in luminal staining
- Decrease in cell height
- Increase in intracellular vacuoles
- Apical epithelial cells with reduction in number/height of microvilli
- Decrease in the height of supranuclear and apical regions of epithelial cells,
- Reduction in number of secretory vesicles in the apical region
Nerve Perturbation Affects Prostate Growth

Fluorogold tracing: analysis of retrograde transport to cell bodies in the DRG and peripheral ganglia

McVary et al. 1998
Gene Expression

Protein Content

Localization
Spontaneous BPH in Aging SHR

A and B: normotensive WKY control

C and D: SHR

Golomb et al., J Androl 21: 58, 2000
Adrenergic Induction of Ventral Prostate Hyperplasia in Mice

A  Saline, 26 d

B  Phenylephrine, 26 d

C  Phenylephrine + α-AR antagonist, 26 d

Marinese et al, Prostate 54:230, 2003
Detrusor Dysfunction in Spontaneously Hypertensive Rats (SHR)

SHR have increased voiding frequency and detrusor overactivity

Increased LUTS With Increased Autonomic Activity

Autonomic Hyperactivity and LUTS

- Hyperinsulinemia
- Obesity-HWR-BMI
- Caloric Intake
- Age
- Physical Inactivity

Increased Sympathetic Tone

- BPH Growth
- BPH Voiding Dysfunction
- Erectile Dysfunction

Increased ED With Increased Autonomic Activity

McVary KT et al., Autonomic Nervous System Overactivity in Men With ED.
Does the concept of a modifiable risk carry any weight?

- Central obesity related pathophysiology
  - Insulin, IGF, leptin, inflammatory markers

- Physical Activity
- Caloric intake/diet type
- Systemic vs. pelvic autonomic tone
- Prostate proliferation (BPH) vs. bothersomeness of symptoms (LUTS)?
- Not mutually exclusive!
Effect of Diet and Exercise on Growth of Prostate Epithelial Cells

- 2 weeks of Pritikin Diet in obese vs. “Trim” cohort (1-28 y)
Intervention Rather than Prevention?

Physical Activity

Caloric Input

Measure LUTS

Obesity with LUTS

Obesity with LUTS

Physical Activity

Caloric Input

Measure LUTS
PDE-5 Inhibitors and LUTS

“My doctor gave me the O.K. to go ahead and die during sex.”
Prevalence of Histologic BPH Increases With Age

Roehrborn CG, McConnell JD.

Major Risk Factors for ED: Aging

Age-Adjusted Progression of ED

- Incidence (%)
- Age (y)
- Complete ED
- Moderate ED
- Minimal ED

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
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</thead>
<tbody>
<tr>
<td>Complete ED</td>
<td>40</td>
<td>48</td>
<td>57</td>
<td>67</td>
</tr>
<tr>
<td>Moderate ED</td>
<td>40</td>
<td>48</td>
<td>57</td>
<td>67</td>
</tr>
<tr>
<td>Minimal ED</td>
<td>40</td>
<td>48</td>
<td>57</td>
<td>67</td>
</tr>
</tbody>
</table>
MSAM-7: Erectile Function Declines With Increasing Severity of LUTS Independent of Age

Average Erectile Function Score (IIEF)*

Base: Men sexually active/sexual intercourse during past 4 weeks, *as measured by IIEF.

Sexual Function Domains
Versus AUA-SI

Sexual Function Domains
Versus TRUS Volume

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
Sustained NO Reduces Smooth Muscle Tension

- Reduced human prostatic smooth muscle tension with SNP
- Reduced canine prostatic smooth muscle tension with SNP

Tension (g/cm²)

-3.5  -2.5  -1.5  -0.5

Human Prostate  Canine Prostate

$P < .005$
Reduced eNOS Staining in Transition Zone

- Reduced intensity of eNOS staining in TZ-BPH tissue compared to the more robust abundance of eNOS protein in epithelial layers from control tissue
- IHC generally used for location not quantitative
- Quantification (Western) absent!

Cyclic Nucleotide PDE Isoenzymes of the Human Prostate

- Most PDEs present in prostate tissue
- PDE-5 and PDE-4 most abundant in prostate transition zone

<table>
<thead>
<tr>
<th>Fraction No.</th>
<th>Pmol cNMP Hydrolized/mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>20</td>
<td>40</td>
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<tr>
<td>30</td>
<td>60</td>
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<tr>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>60</td>
<td>120</td>
</tr>
<tr>
<td>70</td>
<td>140</td>
</tr>
</tbody>
</table>

- cAMP
- cGMP
- cAMP + Ca/CaM
- cAMP + 5 µM cGMP
Immunolocalization of PDE-5 in Human Bladder

PDE-5 Immunolabeling

Control

Concentration of Rodent PDE-5 mRNA in Multiple Organs

* $P<0.01$ vs rat corpus cavernosum

Efficacy of PDE-5 Inhibitors on Rodent Urinary Tract Tissue

Sildenafil for LUTS/BPH ED Trial

No Placebo Run-in

Sildenafil Improves LUTS: IPSS

**Total Irritative Voiding**

- **Placebo (n=162):** 0.00
- **Sildenafil (n=179):** -1.93

**Irritative**

- **Placebo (n=162):** 0.00
- **Sildenafil (n=179):** -0.62

**Voiding**

- **Placebo (n=162):** 0.00
- **Sildenafil (n=179):** -1.46

*P*<0.0001 vs placebo

Tadalafil for LUTS/BPH - IPSS Score

Mean Change

Tadalafil compared to placebo: Tadalafil 2.5mg *P* < .05 at Weeks 4, 8, and 12. Tadalafil 5, 10, and 20 mg *P* < .001 for Weeks 4, 8, and 12. ANCOVA analysis.

*Barry et al. 1995.*
IPSS Changes Stratified by ED History

### No ED History†
- Placebo: Pbo-adj. LS Mean change
  - baseline: 0
  - endpoint: -2.1
- Tad 2.5 mg: Pbo-adj. LS Mean change
  - baseline: 0
  - endpoint: -3.4
- Tad 5.0 mg: Pbo-adj. LS Mean change
  - baseline: 0
  - endpoint: -5.4
- Tad 10.0 mg: Pbo-adj. LS Mean change
  - baseline: 0
  - endpoint: -5.1
- Tad 20 mg: Pbo-adj. LS Mean change
  - baseline: 0
  - endpoint: -4.2

### ED History and Sexually Active
- Placebo: Pbo-adj. LS Mean change
  - baseline: 0
  - endpoint: -2.8
- Tad 2.5 mg: Pbo-adj. LS Mean change
  - baseline: 0
  - endpoint: -4.2
- Tad 5.0 mg: Pbo-adj. LS Mean change
  - baseline: 0
  - endpoint: -4.8
- Tad 10.0 mg: Pbo-adj. LS Mean change
  - baseline: 0
  - endpoint: -5.8
- Tad 20 mg: Pbo-adj. LS Mean change
  - baseline: 0
  - endpoint: -5.6

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*Note:*
†No ED history irrespective of sexual activity

* p<.05 compared to placebo (ANCOVA analysis)
BPH Impact Index Mean Change from Baseline to Endpoint after 4, 8, and 12 Weeks

Tadalafil compared to placebo: tadalafil 5 mg $P<.05$ at Weeks 4 and 12; $P<.001$ at Week 8. Tadalafil 10 mg $P<.001$ at Weeks 4 and 8; $P<.05$ at Week 12. Tadalafil 20 mg $P<.001$ at Weeks 4 and 8; $P<.05$ at Week 12. ANCOVA analysis.

# Qmax (mL/s)

<table>
<thead>
<tr>
<th>Treatment group (n)</th>
<th>Time Point</th>
<th>Mean</th>
<th>Change</th>
<th>Placebo-adjusted LS mean</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (198)</td>
<td>Baseline</td>
<td>10.31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endpoint</td>
<td>11.54</td>
<td>1.23</td>
<td></td>
<td></td>
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<tr>
<td>Tad 2.5 mg (201)</td>
<td>Baseline</td>
<td>9.97</td>
<td></td>
<td></td>
<td>0.17</td>
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<td>Endpoint</td>
<td>11.47</td>
<td>1.50</td>
<td>0.40</td>
<td>0.748</td>
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<tr>
<td>Tad 5 mg (202)</td>
<td>Baseline</td>
<td>10.37</td>
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<tr>
<td></td>
<td>Endpoint</td>
<td>11.98</td>
<td>1.61</td>
<td>0.35</td>
<td>0.832</td>
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<tr>
<td>Tad 10 mg (201)</td>
<td>Baseline</td>
<td>9.93</td>
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<tr>
<td></td>
<td>Endpoint</td>
<td>11.62</td>
<td>1.69</td>
<td>0.72</td>
<td>0.274</td>
</tr>
<tr>
<td>Tad 20 mg (190)</td>
<td>Baseline</td>
<td>9.82</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endpoint</td>
<td>11.97</td>
<td>2.15</td>
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</tbody>
</table>
UDS remained largely unchanged during the study

No statistically significant or clinically adverse

Difference between tadalafil and PL:

\[ P_{\text{det@Qmax}} : \text{mean difference: } -2.2 \text{ cm H}_2\text{O}, \ p = 0.33 \]

\[ Q_{\text{max}}, \ BOOI, \ \text{bladder capacity (all measures } p \geq 0.13) \]
How can NO/NOS hypothesis be valid if urinary flow rates are unchanged?

1. Wrong organ?
2. Bladder compliance/BOO change offset?
3. Central effect?
4. Bladder/prostate perfusion change?
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.
Prostate, Penis and PDE-5:

- Prostate, bladder and penis share regulatory and functional pathways

- Relationship between ED and LUTS remains significant after controlling for risk factors

- LUTS is an independent risk factor for erectile dysfunction

- In vitro and preclinical evidence show that NO-cGMP pathway mediates bladder, urethral, and prostate SM relaxation

- PDE5 is abundant in these tissues, suggesting that a PDE5i may offer a novel approach to relieving LUTS