Urological Aspects in Aging Men

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Urologist

PRIISM  Bruges  25-26 June 2015
What is an aging male?

- What are the (urological) problems of an aging male?
- Who should treat these problems?
Life expectancy is doubled in 100 years

Fig. 21.1. Change in the average life expectancy of men and women in Germany from 1901 to 1992. (Statistisches Jahrbuch 1989, 1994 and 1998, Statistisches Bundesamt Wiesbaden)
Cancer deaths in men: 29.5% of total mortality
Cancer deaths in women: 24.7% of total mortality

Figure 1.2. Age-standardized (European) mortality, all cancers, by sex, Great Britain, 1976–2005.

From Men's Health, Kirby 2009
Over **60%** more men in the age range of 15 to >65 years die from cancers that should affect both men and women equally!

Table 1.1. *Rate ratio of male to female deaths, England and Wales, 2004*

<table>
<thead>
<tr>
<th>ICD-10 code</th>
<th>Site description</th>
<th>Rate ratios, male to female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>All ages</td>
</tr>
<tr>
<td>C00–C97</td>
<td>All cancers</td>
<td>1.14</td>
</tr>
<tr>
<td>C00–C97 excluding C50, C51–C58, C60–C63</td>
<td>All cancers excluding breast and sex-specific cancers</td>
<td>1.37</td>
</tr>
</tbody>
</table>

Mortality Statistics: Cause DH2 No 31
ONS 2004. Londen
From: Men’s Health, Kirby 2009 pg 6
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<tr>
<td>C15</td>
<td>Esophagus</td>
<td><strong>1.90</strong></td>
</tr>
<tr>
<td>C16</td>
<td>Stomach</td>
<td>1.68</td>
</tr>
<tr>
<td>C18–C21</td>
<td>Colon and rectum</td>
<td>1.20</td>
</tr>
<tr>
<td>C22</td>
<td>Liver</td>
<td>1.50</td>
</tr>
<tr>
<td>C25</td>
<td>Pancreas</td>
<td>0.97</td>
</tr>
<tr>
<td>C33–C34</td>
<td>Lung</td>
<td>1.53</td>
</tr>
<tr>
<td>C43</td>
<td>Malignant melanoma of skin</td>
<td>1.31</td>
</tr>
<tr>
<td>C64</td>
<td>Kidney</td>
<td><strong>1.65</strong></td>
</tr>
<tr>
<td>C67</td>
<td>Bladder</td>
<td><strong>2.02</strong></td>
</tr>
<tr>
<td>C71</td>
<td>Brain</td>
<td>1.55</td>
</tr>
<tr>
<td>C82–C85</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>1.16</td>
</tr>
<tr>
<td>C90</td>
<td>Multiple myeloma</td>
<td>1.17</td>
</tr>
<tr>
<td>C91–C95</td>
<td>Leukemia</td>
<td>1.30</td>
</tr>
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</table>
Causes of cancer:

cellmutation on the level of DNA

• Germline (or inherited) factor

• Somatic event: acquired during life
Somatic causes of cancer

- **Smoking**
- **Alcohol use**
- **Overweight and obesity**
- **Lack of physical activities**
- **Urban air pollution**
- **Unsafe sex for women (cervical cancer)**

Danei G, Lancet 2006;366:1784-93
Influence of tobacco on cancer

- 29% of the cancers, mostly lung cancer

but in addition:

- Oral cavity, larynx, pharynx, stomach
- Kidney and bladder
- Pancreas
- Myeloid leukemia
Influence of alcohol on cancer

- a significant factor in both the cause and development of cancer
- Alcohol stimulates angiogenesis
- Ethanol converts to carcinogenic acetaldehyde
- Smoking magnifies the effect of alcohol

Raloff J, Sci News 2006;169:238
O’Hanlon LH, J Natl Cancer Inst 2005;97;1563-4
Table 1.4. Relative risks of alcohol consumption for each cancer site

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Cases</th>
<th>25 g/day</th>
<th>50 g/day</th>
<th>100 g/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity and pharynx</td>
<td>7954</td>
<td>1.8</td>
<td>2.9</td>
<td>6.0</td>
</tr>
<tr>
<td>Esophagus</td>
<td>7239</td>
<td>1.5</td>
<td>2.2</td>
<td>4.2</td>
</tr>
<tr>
<td>Larynx</td>
<td>3759</td>
<td>1.4</td>
<td>1.9</td>
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<tr>
<td>Liver</td>
<td>2294</td>
<td>1.2</td>
<td>1.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>11296</td>
<td>1.1</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Stomach</td>
<td>4518</td>
<td>1.1</td>
<td>1.2</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Prostate</strong></td>
<td>4094</td>
<td><strong>No association</strong></td>
<td>1.1</td>
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Party drinking once a week: 24% by men
13% by women

Men’s Health, Kirby 2009, pg 11
One glas of beer, 5%, =250ml=10 gram
One glas of wine, 12% =100ml=9,6 gram
One glas of liquor, 35% =35ml =9,8 gram
Party drinking once a week: 24% by men  
13% by women  

Men’s Health, Kirby 2009, pg 11

Table 1.4. *Relative risks of alcohol consumption for each cancer site*  

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Late-Life Alcohol Consumption and 20-Year Mortality

Hazard Ratio

Abstainers 2.22
Heavy drinkers 1.70
Light drinkers 1.23
In comparison to moderate drinkers

Abstainers 1.49
Heavy drinkers 1.42
Light drinkers 1.12
In comparison to moderate drinkers

N=1,824; 20 y FU

Influence of Obesity on Cancer

- About 10% of all non-smoking-related deaths by the visceral fat secretion of the “fat-toxins”

Box 1.1. Secretions from visceral fat cells
- Leptin
- Tumor necrosis factor-alpha
- Adiponectin
- Interleukin-6
- Inducible nitric oxide synthase
- Macrophage migration inhibitory factor
- Transforming growth factor-p
- Insulin-like growth factor-1

Eggers H, Urologe 2013;52:1270-1275
Haslam D, Lancet 2005; 399:1197-1209
Influence of Obesity on cancer

Mechanical factors:

- Esophageal cancer due to acid reflux
- Gall bladder cancer

Other factors like low fT, late detection

- Pancreatic cancer
- Kidney cancer: 3KG rise: 7% rise
- Prostate cancer death: BMI: 30-35: 20%
  BMI: 35-40: 34%

Metabolic Syndrome and Prostate cancer

- Complex relationship because MetS has multiple diseases in itself
- Socio-economic factors and access to Public Health: late detection of Prostate Cancer
- Overweight leads to a higher plasmavolume and therefore a lower PSA and later detection
- Data on correlation are controversial
Metabolic Syndrome and Prostate cancer

• From the PCPT study:

if BMI ≥ 40: multiply PSA by 1.7!

Liang Y, BMI adjusted PSA; Urology 76;1268 (2010)
Metabolisches Syndrom und Prostatacarzinom,
Schmitz-Dräger B, Der Urologe 6, 2013 842-846
Metabolic Syndrome and Prostate cancer

- Possible correlation with High-risk Pca
- Less Pca in DM-2
- Metformine could be preventive for Pca
- Higher TG and Chol: worse prognosis/survival
## Statins and Male Sexual Health

**Results:** based on ICD-9-CM
- No contribution to or reduction of:
  - BPH
  - ED
  - Infertility
  - Testicular dysfunction
  - Psychosexual dysfunction

A retrospective cohort analysis

n=20,741 patients
3,302 users
3,302 nonusers

After matching no significant differences in baseline characteristics

Urological (medical) conditions involved in male aging

- Prostate Cancer
- LUTS and BPH
- Erectile disfunction
- LOH (Late Onset Hypogonadism)
Prostate Cancer

• The most prevalent malignancy in men

• The second leading cause of cancer death in men
Prostate Cancer

It is predicted that the number of prostate cancer deaths will increase markedly with an estimated > 500 000 deaths globally in 2020, > 90% among men >70 years

10000 deaths per week!!!!!!
Urological (medical) conditions involved in male aging

- Prostate Cancer
- **LUTS** and **BPH**
- Erectile disfunction
- LOH (Late Onset Hypogonadism)
BPH is the most common benign human neoplasm. Most men live to an age where they have a more than 80% chance of developing histological BPH and a more than 50% chance of being symptomatic from BPH.

BPH seldom reduces the duration of life, but it may impact heavily on his QoL and on those closest to him.
Urological (medical) conditions involved in male aging

- Prostate Cancer
- LUTS and BPH
- Erectile disfunction
- LOH (Late Onset Hypogonadism)
Table 14.1. Prevalence rates of erectile dysfunction in various areas of the world.

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Men (n)</th>
<th>Age (years)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand</td>
<td>2000</td>
<td>1250</td>
<td>40–70</td>
<td>37.5</td>
</tr>
<tr>
<td>Brazil</td>
<td>2001</td>
<td>1286</td>
<td>18–70+</td>
<td>46.2</td>
</tr>
<tr>
<td>France</td>
<td>1997</td>
<td>&gt;1200</td>
<td>18–70</td>
<td>39.0</td>
</tr>
<tr>
<td>Australia</td>
<td>2000</td>
<td>1240</td>
<td>18–91</td>
<td>39.4</td>
</tr>
<tr>
<td>New York State</td>
<td>2000</td>
<td>1650</td>
<td>50–76</td>
<td>46.3</td>
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Complete ED:
1% <40 years
11% >70 years

Moreira ED, Urology 2001;58: 583-8
Life style factors that can lead to ED

- Smoking
- Drugs
- Alcohol misuse
- Overweight
- Lack of physical activities ("use it or lose it")
ED as a sign of other serious diseases

- **Hypertension**
  - 68% of men with hypertension has ED

- **Hyperlipidaemia**
  - 60% of men with ED has dyslipidemia

- **Coronary heart disease**
  - 56% of men with ED has a positive stress test
  - 40% of men with ED has significant stenosis of coronary arteries

Billups K, Friedrich S. Presented at AUA, May 2000; Atlanta, Ga
Pritzker MR. Circulation 1999; 100 (18): I-711.
Men with ED (n=50)

- Significant stenosis in coronary arteries (40%)
- No stenosis (60%)

ED as a first sign of latent insufficiency of the coronary arteries
Diameter of the arteries of the body
Mechanism of smooth muscle relaxation in the corpora cavernosa
Risk factors causing ED

Diabetes, hypertension, lipids, smoking

Nerve terminal

Endothelial cell

NO

NO

Guanylyl cyclase

GTP → cGMP → cGMP-PK → Ca^{++}

Smooth muscle cell

Minimal smooth muscle relaxation

Partial/no erection
Urological (medical) conditions involved in male aging

- Prostate Cancer
- LUTS and BPH
- Erectile disfunction
- LOH (Late Onset Hypogonadism)
Prevalence of Late Onset Hypogonadism

- Population based survey
- N=1475
- Cut off point for Testosterone: 10.4 nmol/l
- Overall prevalence: 5.6%
- Endocrine Society, Bhasin 2010: 6%
- Sharp increase with age

Araujo, 2007
Serum levels of Testosterone and fT decline with age

From the age of 35 years:
about 1.2% fall each year

So: low Testosterone in men:
20% in men over 60 years
30% in men over 70 years
50% in men over 80 years

Harman, 2001

Zitzmann, Nieschlag, 2003
Men with TDS as patients in general practice

Patients with TDS <10.5 nmol/L (%)

- 45–54: 34%
- 55–64: 40%
- 65–74: 40%
- 75–84: 46%
- ≥85: 50%
- All: 39%

n=2162
Prevalence Rates and Odds Ratios for Selected Co-Morbidities in Untreated Hypogonadal Men ≥ 45 Years Visiting a Doctor’s Office

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The Alternative View:

The decline of T in older men is a consequence of the accumulation of comorbidities of aging, which can depress T unrelated to the coincidental non-specific symptoms of chronic disease, that resemble those of LOH.
Alternative hypothesis:

- Decline of T in aging male is not the cause but the consequence of comorbidities

- Is there a “prove” for this theory?

Study of Sartorius, Clinical Endocrinology, 2012, 77, 755-63
Serum testosterone, dihydrotestosterone and estradiol concentrations in older men self-reporting very good health: the healthy man study
Influence of Weight change on Testosterone level

Longitudinal study in a general population: EMAS

n=2736 men; age 40-79 y       FU: 4,4 Y

The role of the urologist

Traditionally, Urology is the leading speciality that is involved in specific care of the aging male.
Men’s Health is a concern for:

• General Practitioners
• Urologists
• Endocrinologist
• Cardiologists
• Sexologists
• Journalists
• Politicians
So:

Men’s Health is not a concern for UROLOGY alone!
No physician can stop aging.

But we can do a lot to reduce the suffering and aches of aging.
Pro-active role

• “If it ain’t broke, don’t fix it”

    to:

• “If you look after it, it doesn’t break!”
While women are geared for preventive care, men generally come for “reparation”
Case: man, 63 years old

History in short:

- Voiding problems since one year
  - urgency
  - frequency 10-12 times
  - nocturia 3-4 times
- No sexual interest
  - “because of voiding problems”
  - morning erections and soloseks: good
- Worried about prostate carcinoma
Case: man, 63 years old

Previous history

- appendectomy; inguinal hernia repair

Medicines:

- atenolol
<table>
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<th>Test</th>
<th>Result</th>
</tr>
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<tbody>
<tr>
<td>Hb</td>
<td>normal</td>
</tr>
<tr>
<td>Kreatinin</td>
<td>normal</td>
</tr>
<tr>
<td>Liverfunctions</td>
<td>normal</td>
</tr>
<tr>
<td>Lipids</td>
<td>normal</td>
</tr>
<tr>
<td>Fasting bloodsugar</td>
<td>normal</td>
</tr>
<tr>
<td>PSA</td>
<td>2.0 ng/ml</td>
</tr>
<tr>
<td>Testosterone</td>
<td>11.0 nmol/l (= 3.17 ng/ml)</td>
</tr>
<tr>
<td>Sed</td>
<td>normal</td>
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Case: man, 63 years old

Physical examination:

- DRT: 30 gram week prostate, no nodule palpable

- External Genitals: normal; volumes: 20 ml

- BMI: 25.6

- Waist circumference: 98 cm
Case: man, 63 years old

What else do you want to know?

What do you do to diagnose?
Case: man, 63 years old

Social history: no depression
- moderate energy
- stress: still working under pressure
- wife: “go to the doctor”

Fluid intake: 2.5 l: 6 coffee, 4 tee
Flow chart: 2500ml / 24 hour
- max capacity: 150-200ml
Case: man, 63 years old

IPSS: 22/4

IIEF: 14

Flow: Qmax: 11 ml/sec
     Voiding volume: 200 ml
     Residual urine: 25 ml
Case: man, 63 years old

TRUS:
Volume: 33ml
Case: man, 63 years old

What is your diagnosis?
Case: man, 63 years old

1. Over Active Bladder (OAB) due to:
   - aging of the bladder (?)
   - inflammation of the prostate(?) / BPH
   - too high fluid intake (coffee/tee)

2. Mild ED, multifactorial:
   - voiding problems
   - atenolol
   - borderline T

3. No sign of prostate carcinoma
Case: man, 63 years old

What to do now?

What is your therapy?
Case: man, 63 years old

1. OAB: - restriction of fluid intake
   - diminish coffee/tee intake
   - start an antimuscarinic: tolterodine
     or an anti-cholinergic: solifenacin

2. ED: - start a PDE-5-inhibitor?
   - change atenolol to valsartan

3. Pca: - reassurance
34 million people in the US: more than hypertension or heart disease
OAB: 1/3 is wet; 2/3 is dry
High costs, significant personal impact: low self esteem, social avoidance
Only 25% seek help!
Results of therapy

### Figure 25.4. Symptom improvement with doxazosin, with and without tolterodine.
BOO, bladder outlet obstruction; OAB, overactive bladder.
From Lee et al.$^{22}$
Testosterone and Sexual Intercourse

From Beta-blocker like atenolol to Angiotensin-1 receptor blocker like valsartan
Quality of live (QoL) of the aging male is largely dependent on the quality of his urological and urogenital functions.
Disease associated with male ageing constitute the majority of all urological OPD visits
General life expectancy and testosterone levels

858 Men (Age ≥ 40 Years; ø 60 Y.)

Total testosterone at 2 assessments

≥ 8,7 nmol/l (n=452)

< 8,7 nmol/l (n=160)

Shores et al. Arch Int Med 2006; 166: 1660
Increase in overweight in 20 years from 30 to 60% The Netherlands; 2009/2010

Blokstra, RIVM 2011
Still a low awareness of the dangers of overweight

Citizens of Alabama came together to raise money for “home for lost animals”
Gender Gap: A general lack of health awareness

Gender difference in life expectancy

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<th>2050</th>
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<tr>
<td>Europe</td>
<td>5.1</td>
<td>8.7</td>
<td>6.4</td>
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<tr>
<td>World</td>
<td>2.7</td>
<td>4.3</td>
<td>4.9</td>
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Men continue to have a higher morbidity and mortality rate than women and life expectancy for men is significantly shorter than that for women in most parts of the world.
# Prevalence Rates and Odds Ratios for Selected Co-Morbidities in Untreated Hypogonadal Patients

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<td>Hyperlipidaemia</td>
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<td>44.4 (25.5 – 64.7)</td>
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<td>1.40 (1.04 - 1.86)</td>
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<td>41.3 (36.4 – 46.2)</td>
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<td>Chronic Pain</td>
<td>38.8 (33.7 – 44.0)</td>
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