Update on diagnosis and complications of adult and elderly male hypogonadism

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Clinical manifestations of male senescence possibly related to hypo-androgenism

- Decreased “general well-being” and “energy level”
- Decreased libido and increased frequency of erectile dysfunction
- Decreased sexual pilosity and skin thickness
- Decreased muscle mass and strength
- Increased fat mass (+altered distribution)
Clinical manifestations of male senescence *possibly* related to hypo-androgenism

- Osteopenia
- Easy sweating; hot flushes
- Decreased red blood cell volume
- *Decreased immunocompetence*
- *Increased cardiovascular risk*
- *Regression cognitive functions*
Symptom-specific threshold testosterone levels for observed increase of prevalence in patients attending an andrology clinic

- Total testosterone (nmol/L):
  - 20
  - 15
  - 10
  - 8
  - 0

- Patients (n):
  - 74
  - 69
  - 65
  - 67
  - 75

- Symptoms:
  - Loss of libido: P<0.001
  - Loss of vigour: P<0.001
  - Obesity: P<0.001
  - Feeling depressed: P=0.001
  - Disturbed sleep: P=0.004
  - Lacking concentration: P=0.002
  - Diabetes mellitus type 2: P<0.001
  - Hot flushes: P<0.001
  - Erectile dysfunction: P=0.003

Increasing prevalence of symptoms with decreasing testosterone concentrations

Zitzmann et al. 4
JCEM 2006;91:4335
Symptoms of hypoandrogenism and low serum testosterone (T)

- High
- Low

Age

- Young
- Old

Increasing prevalence of symptoms and low T

Decreasing specificity of symptoms and low T
Serum testosterone and SHBG vs age (RIA)

Changes in free T distribution with age
Prevalence in function of age of men with low (F)T

Kaufman & Vermeulen  Endocr Rev 2005
according to Vermeulen et al 1996
Evolution serum testosterone over 4yrs in community-dwelling men >70yrs (n=221)

**Total T**
- Total T: -9.5 ng/dL per year (-1.26%)
  - [95% C.I. -12.7; -6.2 ng/dL]

**Bio-T**
- BioT: -6.1 ng/dL per year (-2.43%)
  - [95% C.I. -7.3; -4.9 ng/dL]
SHBG & free testosterone vs age and cohort effects

MONICA Denmark study population
Andersson et al J Clin Endocrinol Metab 92: 4696-4705; 2007
Serum testosterone vs age (LC-MS/MS & GC-MS/MS)

Bhasin et al JCEM 2011
Lower cut-off (percentile 2.5) for T by LC-S/MS in reference group of healthy young nonobese men (from FHS) applied to three cohorts: FHS; MrOS; EMAS

TT<348.3 ng/dl; FT<70pg/ml
Prevalence of symptomatic androgen deficiency in men
Boston Area Community Health (BACH) Survey

Low TT = <300 ng/dl (10.4 nmol/L)

Low FT = <5 ng/dl (0.17 nmol/L)
Identification of late onset hypogonadism (EMAS)

Late-onset hypogonadism can be defined by the presence of at least three sexual symptoms associated with a total testosterone level of less than 11 nmol per liter (3.2 ng per milliliter) and a free testosterone level of less than 220 pmol per liter (64 pg per milliliter).

Prevalence:
- 0.1% 40-49y
- 0.6% 50-59y
- 3.2% 60-69y
- 5.1% 70-79y
Comparison serum testosterone in EMAS by immunoassay versus mass spectroscopy

- Detection of low T (<11nmol/L): 75% sensitivity, 96% specificity

- Diagnosis of hypogonadism (T<11nmol/L + FT< 0.220nmol/L + 3 sexual symptoms): 86% sensitivity, 9% specificity

Huhtaniemi et al EJE 203;166:983-991
Mixed testicular and hypothalamic factors in Late Onset Hypogonadism

Leydig cells
Age-related changes and modifiable risk factors

EMAS study population

Wu et al J Clin Endocrinol Metab 93:2737; 2008
Decreased mean testicular volume (by 31%)

Mahmoed et al. JCEM 2003;88:179

Total testicular volume (mL)

Frequency (%)
Decreased number of Leydig cells

y = 644 - 6.8 x
rho = -0.62

Neaves et al. JCEM 55:756; 1984
LH pulsatility in young and elderly men (representative profiles)

Age 23

Age 83
Presentation of hypogonadism in EMAS
Age-related changes and modifiable risk factors EMAS study population
Effect of obesity on serum testosterone

MMAS study population

(a) Overweight (BMI ≥ 25 kg/m²)

(b) Obesity (BMI ≥ 30 kg/m²)

Mohr et al EJE155:443-452;2006
Summary diagnosis of hypogonadism: well established low T?

- Cut-off around <11nmol/L (= 320ng/dl) for total T & <0.225nmol/L (= 6.5 ng/dl) for freeT
- Well validated immunoassay acceptable for clinic
- Blood sampling before 10 a.m
- Consider freeT when factors affecting SHBG (e.g. obesity; glucocorticoids,....) and when borderline total T
- Elevated gonadotropins, if present can help establish diagnosis
- Low (free)T to be confirmed on second occasion, ideally with few weeks interval (cfr possible transient reversible cause)
Summary diagnosis of hypogonadism: signs/symptoms?

- Spontaneously reported symptoms (= reason for consultation) more reliable than ‘sollicited’ by questioning: avoid to use for diagnostic purpose screening questionnaires with poor specificity

- Cluster of symptoms more reliable

- More specific significance of sexual symptoms (?)

- Consider alternative causes for reported symptoms
Consequences of hypogonadism

- Adiposity, insulin resistance, metabolic sy, type2 diabetes
- Sexual function
- Bone
- Muscle, mobility
- Cardiovascular disease, mortality
Association of SHBG and T with the metabolic syndrome

Kupelian et al. J Clin Endocrinol Metab 2008;93:3403-10
Fifty-two-Week Treatment With Diet and Exercise Plus Transdermal Testosterone Reverses the Metabolic Syndrome and Improves Glycemic Control in Men With Newly Diagnosed Type 2 Diabetes and Subnormal Plasma Testosterone

ARMIN E. HEUFELDER,* FARID SAAD,†‡ MATHIJS C. BUNCK,§ AND LOUIS GOORENS

Diet + exercise

Diet + exercise + T (50mg gel)

J Andrology 2009;30:726-36
### Meta-analysis treatment effects on sexual function

Isidori et al 2005  
Clin Endo 63:381

<table>
<thead>
<tr>
<th>Sexual Domain</th>
<th>Studies</th>
<th>Standardised mean difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning Erections</td>
<td>Davidson et al. (1979)¹⁸, Carari et al. (1990)²², Dobs et al. (1998)²³, Cavallini et al. (2004)²²</td>
<td>2.64 (1.02, 4.26)</td>
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<td></td>
<td></td>
<td>2.47 (0.91, 4.04)</td>
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<td></td>
<td></td>
<td>0.93 (–0.23, 2.06)</td>
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<td></td>
<td></td>
<td>1.59 (1.10, 2.08)</td>
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<td></td>
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<td>1.53 (1.00, 2.07)</td>
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<tr>
<td>Erectile function</td>
<td>Skakkebaek et al. (1981)¹⁷</td>
<td>1.58 (0.69, 2.51)</td>
</tr>
<tr>
<td></td>
<td>Seidman et al. (2001)²⁴</td>
<td>2.58 (1.58, 3.59)</td>
</tr>
<tr>
<td></td>
<td>Steidle et al. (2003)²⁶</td>
<td>0.35 (0.08, 0.61)</td>
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<td></td>
<td>Cavallini et al. (2004)²²</td>
<td>3.04 (2.41, 3.67)</td>
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<td>1.87 (0.31, 3.43)</td>
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<td>Intercourses</td>
<td>Skakkebaek et al. (1981)¹⁷</td>
<td>2.00 (1.01, 2.99)</td>
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<tr>
<td></td>
<td>Bancroft and Wu (1983)³⁰</td>
<td>0.69 (–0.32, 1.71)</td>
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<tr>
<td></td>
<td>Kwan et al. (1985)¹⁹</td>
<td>1.75 (0.26, 3.75)</td>
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<td></td>
<td>Carani et al. (1990)²²</td>
<td>3.50 (1.59, 5.41)</td>
</tr>
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<td></td>
<td>Dobs et al. (1998)²³</td>
<td>0.09 (–1.01, 1.18)</td>
</tr>
<tr>
<td></td>
<td>Seidman et al. (2001)²⁴</td>
<td>1.04 (0.26, 1.83)</td>
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<td>1.19 (0.54, 1.85)</td>
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<tr>
<td>Sexual Motivation</td>
<td>Skakkebaek et al. (1981)¹⁷</td>
<td>2.33 (1.28, 3.39)</td>
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<td></td>
<td>Bancroft et al. (1983)³⁰</td>
<td>1.33 (0.23, 2.42)</td>
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<tr>
<td></td>
<td>Carani et al. (1990)²²</td>
<td>3.21 (1.41, 5.02)</td>
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<tr>
<td></td>
<td>Dobs et al. (1998)²³</td>
<td>–0.35 (–1.45, 0.75)</td>
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<td></td>
<td>Steidle et al. (2003)²⁶</td>
<td>0.38 (0.11, 0.64)</td>
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<td>1.06 (0.25, 1.86)</td>
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<td>Sexual Satisfaction</td>
<td>Skakkebaek et al. (1981)¹⁷</td>
<td>2.00 (1.01, 2.99)</td>
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<tr>
<td></td>
<td>Seidman et al. (2001)²⁴</td>
<td>0.17 (–0.56, 0.90)</td>
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<td></td>
<td>Cavallini et al. (2004)²²</td>
<td>2.18 (1.64, 2.72)</td>
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<td></td>
<td>1.16 (0.04, 2.29)</td>
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<tr>
<td>Sexual Thoughts</td>
<td>Skakkebaek et al. (1981)¹⁷</td>
<td>1.57 (0.65, 2.50)</td>
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<tr>
<td></td>
<td>Bancroft and Wu (1983)³⁰</td>
<td>0.97 (–0.07, 2.01)</td>
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<tr>
<td></td>
<td>Carani et al. (1990)²²</td>
<td>2.00 (0.57, 3.43)</td>
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<td></td>
<td>Steidle et al. (2003)²⁶</td>
<td>0.36 (0.09, 0.62)</td>
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<td></td>
<td>Cavallini et al. (2004)²²</td>
<td>3.19 (2.55, 3.84)</td>
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<td></td>
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<td>1.60 (0.29, 2.92)</td>
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<tr>
<td>Total Erection</td>
<td>Davidson et al. (1979)¹⁸</td>
<td>3.14 (1.36, 4.93)</td>
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<tr>
<td></td>
<td>Skakkebaek et al. (1981)¹⁷</td>
<td>2.50 (1.41, 3.55)</td>
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<tr>
<td></td>
<td>Carani et al. (1990)²²</td>
<td>0.91 (–0.29, 2.11)</td>
</tr>
<tr>
<td></td>
<td>Steidle et al. (2003)²⁶</td>
<td>0.61 (0.34, 0.88)</td>
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<td></td>
<td></td>
<td>1.40 (0.54, 2.26)</td>
</tr>
</tbody>
</table>
Dose-Dependent Effects of Testosterone on Sexual Function, Mood, and Visuospatial Cognition in Older Men

Gray et al JCEM 2005
Bone loss during chemical castration with GnRH analogs in prostate cancer

Mittan et al., J Clin Endocrinol Metab 2002;87:3656
Denosumab in Men Receiving Androgen-Deprivation Therapy for Prostate Cancer

Denosumab in Men Receiving Androgen-Deprivation Therapy for Prostate Cancer

Figure 3. Cumulative Incidence of New Vertebral Fracture at 12, 24, and 36 Months, According to Study Group.

The relative risk for vertebral fracture among 679 patients in the denosumab group as compared with 673 patients in the placebo group was 0.15 at 12 months, 0.31 at 24 months, and 0.38 at 36 months.

Bone loss vs Bioavailable E$_2$ in elderly men >70y

Van Pottelbergh et al
JCEM 2003
Yearly incidence of fracture as a function of serum estradiol in MrOs Sweden

Mellström et al JBMR 23:1553; 2008
CVD and MORTALITY
Endogenous T vs all cause & cardiovascular mortality
EPIC-NORFOLK study (Khaw et al Circulation 2007)

**Figure.** Multivariate-adjusted survival by quartile group of endogenous testosterone concentrations (1 is lowest, 4 is highest) in 2314 men 42 to 78 years old in EPIC-Norfolk 1993 to 2003.
Low free T predicts mortality from CVD: The Health in Men Study

Hyde et al  J Clin Endocrinol Metab 2012;97:179-89
Meta-analyses endogenous T vs mortality/CVD

Araujo et al J Clin Endocrinol Metab 2011

Conclusion: Low endogenous testosterone levels are associated with increased risk of all-cause and CVD death in community-based studies of men, but considerable between-study heterogeneity, which was related to study and subject characteristics, suggests that effects are driven by differences between cohorts (e.g. in underlying health status). (J Clin Endocrinol Metab 96: 3007–3019, 2011)

Ruige et al Heart 2011

- In healthy middle aged men, testosterone does not predict cardiovascular disease (CVD).
- In elderly men, low testosterone predicts increased risk for CVD and/or mortality. It is at present unclear whether low testosterone has a direct negative effect, or whether it should be regarded as ‘marker of poor health’.
- Recent studies on testosterone and CVD/mortality show more pronounced associations than earlier studies.
Endogenous E2 and CVD: meta-analysis of prospective studies

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(risk ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Risk ratio IV, Random, 95% CI</th>
<th>Risk ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cauley et al</td>
<td>-0.073</td>
<td>0.362</td>
<td>8.1%</td>
<td>0.93 (0.46 to 1.89)</td>
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<tr>
<td>Yarnell et al</td>
<td>0.277</td>
<td>0.175</td>
<td>13.0%</td>
<td>1.32 (0.94 to 1.86)</td>
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<tr>
<td>Mikulec et al</td>
<td>-0.061</td>
<td>0.089</td>
<td>15.1%</td>
<td>0.94 (0.79 to 1.12)</td>
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<tr>
<td>Arnlov et al</td>
<td>-0.4</td>
<td>0.157</td>
<td>13.5%</td>
<td>0.67 (0.49 to 0.91)</td>
<td></td>
</tr>
<tr>
<td>Abbott et al</td>
<td>1.18</td>
<td>0.31</td>
<td>9.3%</td>
<td>3.25 (1.77 to 5.98)</td>
<td></td>
</tr>
<tr>
<td>Nilsson et al</td>
<td>0.343</td>
<td>0.467</td>
<td>6.1%</td>
<td>1.41 (0.56 to 3.52)</td>
<td></td>
</tr>
<tr>
<td>Tivesten et al</td>
<td>-0.301</td>
<td>0.302</td>
<td>9.5%</td>
<td>0.74 (0.41 to 1.34)</td>
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<tr>
<td>Vikan et al</td>
<td>-0.02</td>
<td>0.237</td>
<td>11.3%</td>
<td>0.98 (0.62 to 1.56)</td>
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<tr>
<td>Akishita et al</td>
<td>0.165</td>
<td>0.758</td>
<td>3.0%</td>
<td>1.18 (0.27 to 5.21)</td>
<td></td>
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<tr>
<td>Menke et al</td>
<td>-0.821</td>
<td>0.243</td>
<td>11.1%</td>
<td>0.44 (0.27 to 0.71)</td>
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</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.98 (0.74 to 1.31)</strong></td>
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</table>

Heterogeneity: $\tau^2 = 0.14; \chi^2 = 35.68, df = 9 (p<0.0001); I^2 = 75\%$

Test for overall effect: $Z = 0.13 (p=0.90)$

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Vandenplas et al Heart 2012;98:148-82
Prevalence and incidence of mobility limitations in the Framingham Offspring Study

Krasnoff et al JCEM 95:2790; 2010
Increased risk of incident falls in men with lower freeT amongst 2587 community-dwelling men 65-99y

<table>
<thead>
<tr>
<th>Median Free Testosterone Value in Each Quartile, ng/dL</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.17</td>
<td>1.0</td>
</tr>
<tr>
<td>6.77</td>
<td>1.0</td>
</tr>
<tr>
<td>7.95</td>
<td>1.0</td>
</tr>
<tr>
<td>9.82</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Orwoll et al. Arch Intern Med 2006;166:2124

• No association with FT > 80y!
Low freeT predicts frailty in older men
Transdermal T (50mg/day) in intermediary-frail and frail elderly (T< 12nmol/l or FT <250pmol/l)

Remark:
O’Connel et al JCEM 2011

Srinivas-Shankar et al JCEM 95:639; 2010
Change Skeletal Muscle Mass

![Graph showing change in skeletal muscle mass with T.E. dose (mg/week)]

- **Dose effect**: $P<0.0001$
- **Age effect**: $P=NS$

Change Leg Press Strength 1 RM

![Graph showing change in leg press strength with T.E. dose (mg/week)]

- **Dose effect**: $P=0.008$
- **Age effect**: $P=0.84$
**Change in Hemoglobin**

- **Dose effect**: $P=0.01$
- **Age effect**: $P=0.0015$

**Change in HDL-Cholesterol**

- **Dose effect**: $P<0.022$
- **Age effect**: $P=0.67$

Bhasin et al.  
JCEM 2005;90:678
Adverse Events Associated with Testosterone Administration

CONCLUSIONS AND RELEVANCE  Among a cohort of men in the VA health care system who underwent coronary angiography and had a low serum testosterone level, the use of testosterone therapy was associated with increased risk of adverse outcomes. These findings may inform the discussion about the potential risks of testosterone therapy.
Figure 2. Kaplan-Meier Survival Curves With Testosterone Therapy Evaluated as a Time-Varying Covariate

Survival, %

No testosterone therapy
Testosterone therapy

HR, 1.29 (95% CI, 1.04-1.58)
Log-rank P = .02

Days

No. at risk
Testosterone therapy

|       | No    | Yes
<table>
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<tr>
<td>HR</td>
<td>8709</td>
<td>0</td>
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<tr>
<td>Testosterone therapy</td>
<td>5337</td>
<td>439</td>
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<td></td>
<td>2897</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td>918</td>
<td>233</td>
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<td></td>
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<td>61</td>
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</table>

Vigen et al JAMA 2013; 310:1829-36
T treatment and mortality in men with low T (observational data)

Fig. 1. Unadjusted Kaplan-Meier survival curves illustrate that testosterone-treated men had a longer survival time than untreated men ($P = 0.029$).

Shores et al J Clin Endocrinol Metab 2012;97: 2050-58
Who should we consider for treatment?

- Established hypogonadism in young men will usually be treated unless contra-indications even though there is understandably little data from controlled trials in young men.

- Positive findings in the elderly largely limited to elderly with initially low serum testosterone.

- Unknown longer term risk/benefit.
Who should we consider for treatment?

- Free testosterone frankly below normal for the young
- Unequivocal signs and symptoms of hypogonadism (preferably spontaneously reporting)
- No reversible cause
- No contra-indications
- Consider also the alternatives alternatives first if only low total testosterone!
- Remarks: dosage; monitoring; treatment interrupted
Thank You