CARDIOMETABOLIC DISEASE AND TESTOSTERONE DEFICIENCY: IS THERE A LINK?

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History of Testosterone

- 1935- Isolated and synthesized from cholesterol
- 1939 Nobel Prize- Butenandt and Ruzicka
- 1940-60 Golden Age of Steroids
- Many uses promoted- eg, cardiac, anemia
- Use then became limited
  - Hepatotoxicity of oral, alkylated T (S Chopra JAMA 1978)
  - Major concern: prostate cancer
T therapy in the late 1980s

- Minimal clinical experience
  - Congenital/genetic issues, eg Klinefelter’s
  - Pituitary tumors/resection
  - Absent testes (cancer, trauma)
- Treatment: T injections q 4 wks
- The big fear: Prostate cancer
Production of Testosterone

Hypothalamus

Pituitary

Testis

Testosterone

GnRH

LH

FSH

Sperm

GnRH=gonadotropin-releasing hormone; LH=luteinizing hormone; FSH=follicle-stimulating hormone.

LH receptor

LEYDIG CELL

LH

cAMP

Cholesterol

Pregnenolone

T

To peripheral target tissue

E<sub>2</sub>

DHT

T

Aromatase

5α-Reductase

To seminiferous tubules
Prevalence of Hypogonadism

Baltimore Longitudinal Study on Aging (BLSA)

Men (%) in Hypogonadal Range

N = 890

<table>
<thead>
<tr>
<th>Age</th>
<th>Total Testosterone</th>
<th>Free T index</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>(n=279)</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>(n=332)</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>(n=350)</td>
<td></td>
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<tr>
<td>70-79</td>
<td>(n=251)</td>
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</tbody>
</table>

Testosterone and Age

Wu et al, JCEM 93:2737, 2008
Diagnosis of hypogonadism

- Controversial
- Confusing diagnosis
- Many tests, many published thresholds
  - Total T, free T, bioavailable T, free androgen index (FAI)
  - Total T < 200, < 300, or < 348 ng/dl?
Diagnosis of hypogonadism

- A clinical syndrome
- Characteristic symptoms and signs
- Associated with reduced T levels
Sexual symptoms of low T

- Diminished libido
- ED
- Change in orgasm experience
- Delayed or absent orgasm
- Reduced ejaculate volume
Non-sexual symptoms of low T

- Mood
- Decreased muscle mass/strength
- Increased fat (abdominal)
- Vitality/energy/fatigue/motivation
Signs of low T

- Decreased bone density
- Body composition
- Anemia
Hypogonadism in Men (HIM) study

- 2162 men
- Men >45y
- Study performed in men in waiting rooms of physician’s offices, mainly primary care
- 38.7% had T<300ng/dl

Prevalence of Low Testosterone in Other Conditions

- Obesity: 52%
- Diabetes: 50%
- AIDS: 50%
- Hypertension: 42%
- Hyperlipidemia: 40%
- Chronic Opioid Use: 74%
- ED: 36%

AIDS = acquired immune deficiency syndrome
ED = erectile dysfunction

Low T strongly associated with:

- Abdominal obesity
- Elevated fasting glucose
- Insulin resistance
- Dyslipidemia
- Hypertension
T Therapy Improves Metabolic Syndrome Components

↓ FBG
↓ HbA1c
↓ Fasting insulin
↓ HOMA index of insulin resistance
↓ Waist circumference, BMI, cholesterol
↓ Prevalence of metabolic syndrome (after 1 year)

- 3-month trial

- 12-month trial


*United Kingdom
†Germany

FBG=fasting blood glucose
HbA1c=glycosylated hemoglobin
PREVALENCE OF HYPOGONADISM (TT < 300 ng/dl)

BY BMI IN 1687 AMBULATORY MEN

Low Total Testosterone and Low SHBG levels independently predict development of the metabolic syndrome and diabetes in middle-aged men.

Metabolic syndrome prospectively identifies risk for CHD and even more strongly predicts new-onset diabetes.

**SHBG**=sex hormone-binding globulin

Putative Effects of Testosterone on Stem Cell Differentiation in Muscle Tissue


With permission from Abdul Traish, PhD
Manifestations of Androgen Deficiency in Visceral Fat

With permission, From Abdul Traish, PhD
Fracture Rates by Age and Gender

Donaldson LF, et al. *J Epidemiol Community Health* 1990;44:241-245
Osteoporosis in Men

- 66% of men with hip fractures had hypogonadism
- Direct effect, and also via conversion to estradiol (E2)
- Cortical bone loss in men occurs in association with decreases in bioavailable testosterone and estrogen (Riggs BL et al, J Bone Miner Res 2008; 23:205)
- T deficiency associated with reduced osteoblast function

Gullberg B et al, Osteoporos Int 1997; 7:407
Jiang HX et al, J Bone Miner Res 2005;20:494
Kanis JA et al, Osteoporos Int 2005;16:581
Prevalence of Osteoporosis in Men with Symptomatic Testosterone Deficiency

- 229 consecutive patients with low T
- Mean patient age was 50.2 ± 12.3 years (range 19-80)
- Osteoporosis in 10%

Free Testosterone <1.0ng/dL

- Osteoporotic
- Non-Osteoporotic

Free Testosterone >1.0ng/dL

- Osteoporotic
- Non-Osteoporotic

P=0.006

Conners et al, Abstract #83, SMSNA 2009
Low Testosterone Levels Associated With Increased Mortality

Serum Testosterone and Mortality in Male Veterans

Log-rank test; \( \chi^2 = 14.4, P = .001 \).


Slide courtesy of Glenn R. Cunningham, MD.
CUMULATIVE SURVIVAL BASED ON BIOAVAILABLE T
N=930 MEN WITH CORONARY HEART DISEASE
FOLLOWED FOR 6.9 ± 2.6 Y
MORTALITY: LOW T 21%, NORMAL T 12%

Log rank, p=0.007, HR 2.2 (1.2-3.9)

Low T As A Predictive Marker For Cardiovascular Mortality

- N = 11,606 men (no cancer or CVD)
  - 825 men died matched with 1489 living men in control group
- Mean follow-up 7 years
- “In men, endogenous testosterone concentrations are inversely related to mortality due to cardiovascular disease and all causes”

Overall mortality

$P < .001$ for trend after adjusting for multiple variables, including age, BMI, blood pressure, cigarette smoking, etc.

SURVIVAL IN 587 MEN WITH TYPE 2 DM OVER 5.8Y BASED ON SERUM T

Hazard Ratio = 1.4 p = 0.015 for Normal and Low TT

## Low Testosterone and Increased Mortality (N >500)

<table>
<thead>
<tr>
<th>Recent Studies</th>
<th>HR (95% CI)</th>
<th>Nature</th>
<th>Men, n</th>
<th>Follow-up, y</th>
<th>Mortality</th>
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<tbody>
<tr>
<td>Shores, 2006</td>
<td>1.88 (1.34–2.63)</td>
<td>Retrospective</td>
<td>858</td>
<td>8</td>
<td>All-cause</td>
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<td>Laughlin, 2008</td>
<td>1.38 (1.02–1.85)</td>
<td>Prospective</td>
<td>794</td>
<td>20</td>
<td>CVD</td>
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<td>Khaw, 2007</td>
<td>2.29 (1.60–3.26)</td>
<td>Prospective</td>
<td>2314 of 11,606</td>
<td>10</td>
<td>All-cause and CVD</td>
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<td>Haring, 2010</td>
<td>2.32 (1.38–3.89)</td>
<td>Prospective</td>
<td>1954</td>
<td>7.2</td>
<td>All-cause</td>
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<td></td>
<td>2.56 (1.15–6.52)</td>
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<td>CVD</td>
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<td>Malkin, 2010</td>
<td>2.27 (1.45–3.60)</td>
<td>Prospective</td>
<td>930</td>
<td>6.9</td>
<td>All-cause in men with coronary disease</td>
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<td>Tivesten, 2009</td>
<td>1.65 (1.29–2.12)</td>
<td>Prospective</td>
<td>3014</td>
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<td>Menke, 2010</td>
<td>1.43 (1.09–1.87)</td>
<td>Prospective</td>
<td>1114</td>
<td>9</td>
<td>All-cause</td>
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<td>Vikan, 2009</td>
<td>1.24 (1.01–1.54)</td>
<td>Prospective</td>
<td>1568</td>
<td>11.2</td>
<td>All-cause</td>
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<td>Corona, 2010</td>
<td>7.1 (1.8–28.6)</td>
<td>Prospective</td>
<td>1687</td>
<td>4.3</td>
<td>CVD</td>
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</tbody>
</table>
Survival of treated vs untreated T-deficient men

- N=1031
- Men>40y
- T<250 ng/dl
- Mortality:
  - 10.3% T treated
  - 20.7% untreated
  - P<0.0001

Shores et al, JCEM 2012
Androgen Deficiency

- Diabetes & Insulin Resistance
- Obesity
- Lipids
- Metabolic Syndrome
- Muscle Mass

- Oxidative stress
- Endothelial dysfunction
- Inflammatory factors/ Proliferation

Atherosclerosis, Cardiovascular Disease & Erectile Dysfunction

With permission, from Abdul Traish
Global Pooled Longitudinal Study of Hormones and PCa Risk

- 3886 men with PCa
- 6448 age-matched controls
- No significant relationship between androgens and PCa
- Highest 20% T vs lowest 20% - no difference

Roddam et al, JNCI 2008;100(3):170-183
T and Prostate Cancer

- Meta-analysis of 19 placebo-controlled T therapy studies in men with low or low-nl T
- Comparison of men treated with T vs placebo revealed no difference in:
  - PCa
  - PSA > 4.0 ng/ml
  - Urinary symptom scores

Calof et al, J Gerontology 2005;60A:1451-7
T AND PROSTATE CANCER IN PLACEBO ARM OF REDUCE TRIAL

- 3255 men
- Prostate biopsies at 2y and 4y
- No association between PCa risk and serum T or DHT
- Men with high T at no greater PCa risk

Muller et al, European Urology, 2012
Saturation Model

Prostate cancer growth/PSA

Androgen-dependent growth

Androgen-independent growth

Serum Testosterone

Saturation: 
T for PCa is like “water for a thirsty tumor”

Once the “thirst” has been quenched, additional T has no further effect
T therapy in men with untreated PCa

- T therapy in 13 men with untreated PCa (surveillance)
- Median duration T therapy 2.5y (1-8y)
- All with follow-up biopsies (avg 2/person)

Morgentaler et al, J Urol 2011
T therapy in men with untreated PCa

- All men experienced symptomatic benefit
- No increase in PSA
- No increase in prostate volume
- No definite cancer progression
- 54% of biopsies - no cancer seen

Morgentaler et al, J Urol 2011
T and Cardiometabolic Disease

- T appears to play a key role at multiple levels in cardiometabolic disease
- A normal serum T is associated with better health and increased longevity
- Serum T (or free T) may be the most important indicator of overall male health
- Better than cholesterol, glucose, PSA