Diagnosis and Clinical Evaluation of Hypogonadism in Adult Patients with Obesity and Diabetes

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Outline

• General background
• Serum sex hormones in glucose intolerance, DM and metabolic syndrome
• Mechanisms to explain reduced serum T levels
• Effects of testosterone therapy in men with DM
Frequency of Sexual Relationships based on Age
(Kinsey, 1963)
PERCENTAGE OF MEN IN DIFFERENT AGE GROUPS WHO ARE IMPOTENT

Source: Baltimore Longitudinal Study of Aging

PERCENTAGE OF IMPOTENT MEN

- 20-39: 7.5%
- 40-49: 11%
- 50-59: 18%
- 50-64: 38%
- 65-79: 57%
Questions to Evaluate Sexual Function in Men and Women

• Both genders
  – Change in libido
  – Ability to reach orgasm
  – Signs and symptoms of hypogonadism

• Men
  – Ability to attain an erection with different partners or masturbation
    – (Morning vs. sexual erections)

• Women
  – Vaginal dryness
Chronic Illnesses Associated With Erectile Dysfunction

- Systematic diseases:  
  - Atherosclerosis
  - Diabetes Mellitus
  - Renal Failure
  - Hepatic failure

- Neurogenic diseases:  
  - Alzheimer’s disease

- Penile disorders:  
  - Peyronie’s disease

- Psychiatric disorders:  
  - Depression
  - Performance Anxiety
  - Hyperthyroidism
  - Hypothyroidism
  - Hypogonadism
  - Hyperprolactinemia

- Endocrine disorders:
Increased frequency and lower age of onset of erectile dysfunction in type II DM vs non-diabetics.
Plasma Testosterone Levels During the Life Cycle in Men

Increased Risk of Erectile Dysfunction with Worsening Glycemic Control

Weinberg, The Journal of Sexual Medicine, 8 SEP 2013
Incident CVD in Men With ED and No Prior Cardiovascular Event

- 7-y estimate of cardiovascular events approaching 15%

- Of 8063 men without CVD at study entry, 3816 (mean age, 62 y) had ED

- Among 4247 men without ED at study entry, 2420 reported incident ED after 5 y

CVD, cardiovascular disease; ED, erectile dysfunction.
ED Predicts Coronary Events: 10-Year Follow-up

- 1,402 men aged 40 to ≥70 y with no known CAD
- ED and CAD may share common underlying vascular pathology
- ED in younger men related to marked increase in risk of cardiac events
- ED in older men of little prognostic importance

ED Predicts Coronary Events: 10-Year Follow-up

- 2115 men from Olmstead County Study of Urinary Symptoms and Health Status Among Men
  - 1402 (66%) aged 40 to ≥70 y with sexual partner and no known CAD at study entry
  - 156 CAD events
- ED and CAD may share common underlying vascular pathology
- ED in younger men related to marked increase in risk of cardiac events
- ED in older men of little prognostic importance

CAD, coronary artery disease; ED, erectile dysfunction.

Chew et al Study: Population and Design Highlights

- 2318 men with ED from Western Australia Erectile Dysfunction Research Dataset (WAEDRD)
  - 1660 with no CVD prior to ED included in study cohort
- Followed for development of CVD
  - 308 CVD events
- Retrospective, linked-data cohort
- IRR is ratio of incidence in study population versus general population - incidence of CVD in ED population divided by incidence of CVD in general male population

Stronger Relationship Between ED and CVD in Young Men

ED and testosterone deficiency are independently distributed disorders.

- Between 2.1% and 21% of men with ED have low levels of serum testosterone, depending on the test used to measure testosterone.


ED = erectile dysfunction.
Production and Regulation of Testosterone

Only 2% is free testosterone; 98% is bound

# Types of Hypogonadism Include

<table>
<thead>
<tr>
<th>Primary (congenital or acquired)</th>
<th>Hypogonadotropinic (congenital or acquired)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testicular failure due to conditions such as</td>
<td>Idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency</td>
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<tr>
<td>• Cryptorchidism</td>
<td>• Pituitary-hypothalamic injury from tumors, trauma, or radiation</td>
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<tr>
<td>• Bilateral torsion</td>
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<tr>
<td>• Orchitis</td>
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<tr>
<td>• Vanishing testis syndrome</td>
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<tr>
<td>• Orchiectomy</td>
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<tr>
<td>• Klinefelter syndrome</td>
<td></td>
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<tr>
<td>• Chemotherapy</td>
<td></td>
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<tr>
<td>• Toxic damage from alcohol, heavy metals</td>
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</tbody>
</table>

- **These men usually have**
  - Low serum testosterone concentrations
  - Gonadotropins (FSH and LH) above the normal range

- **These men have**
  - Low serum testosterone concentrations
  - Gonadotropins in the normal or low range
Challenges in Measuring Serum Total or Free Testosterone

- Variability in serum testosterone levels due to biology, circadian rhythms, and laboratory assays
- LC-MSMS represented the gold standard test in a study comparing different laboratory methods for measuring total testosterone
- Total testosterone less than 150 ng/dL had specificity >95%, but needed a level of the threshold value for total testosterone must exceed 350–400 ng/dL; the sensitivity of a test using this threshold was 97%–98%.
Conditions Associated with Disturbances in SHBG

- Reduced SHBG - Reduced total T, but possibly normal free and bioavailable T
  - Type 2 DM
  - Obesity
  - Insulin Resistance
- Increased SHBG - Increased total T, but possibly normal free and bioavailable T
  - Aging
  - HIV, hepatitis
Male Hormonal Status Changes With Age as SHBG Increases

As SHBG increases with age, levels of free testosterone decrease

Effects of Aging on Hormone Levels

Massachusetts Male Aging Study (MMAS)

![Graph showing trends in hormone levels across different aging stages.](image)

Trend
- Cross-sectional, baseline, N=1709
- Cross-sectional, follow-up, N=1156
- Longitudinal

Hypogonadism Signs and Symptoms

Endocrine Society guidelines¹

- Decreased spontaneous erection
- Diminished libido and sexual activity
- Breast discomfort, gynecomastia
- Loss of axillary and pubic hair, reduced shaving
- Very small or shrinking testes
- Low or zero sperm count
- Height loss, low trauma fracture, low bone mineral density
- Hot flushes, sweats
- Depressed mood, dysthymia
- Poor concentration and memory
- Sleep disturbance, increased sleepiness
- Mild anemia
- Reduced muscle bulk and strength
- Increased body fat, body mass index

European Male Aging Study: Only 3 sexual symptoms had syndromic association with decreased testosterone levels: poor morning erection, low sexual desire, and erectile dysfunction²

Present in 2% of the 3300 men

New Thoughts on Male Hypogonadism

- Acquired causes of male hypogonadism
  - Aging
  - Acute illness
  - Chronic renal failure
  - Hemochromatosis
  - HIV
  - Obesity
  - Diabetes mellitus
  - Metabolic syndrome
  - Glucocorticoids
  - Cancer

- Likely benefits from testosterone Tx
  - Sexual dysfunction
  - Osteoporosis
  - Depression
  - Fatigue
  - Wasting syndromes (AIDS)
  - Reduced muscle mass
Prevalence of Low Testosterone in Other Conditions

- Chronic opioid use for pain: 74%
- Obesity: 52%
- Diabetes: 50%
- AIDS (HIV 30%): 50%
- Hypertension: 42%
- Hyperlipidemia: 40%
- ED: 19%

ED = erectile dysfunction

## Endocrine Society Guidelines for Screening for Low T

- Screening for low T is not recommended in all patients

### Recommended Patients to Screen

<table>
<thead>
<tr>
<th>Type 2 diabetes mellitus</th>
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<tbody>
<tr>
<td>Treatment with medications, including opioids and glucocorticoids</td>
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<tr>
<td>HIV-associated weight loss</td>
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<tr>
<td>End-stage renal disease and maintenance hemodialysis</td>
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<tr>
<td>Moderate to severe chronic obstructive lung disease</td>
</tr>
<tr>
<td>Sexual dysfunction or Infertility</td>
</tr>
<tr>
<td>Osteoporosis or low trauma fracture</td>
</tr>
<tr>
<td>Sellar mass</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
</tr>
</tbody>
</table>

### NOT Recommended to Screen

- General population
Outline

• General background
• Serum sex hormones in glucose intolerance, DM and metabolic syndrome
• Mechanisms to explain reduced serum T levels
• Effects of testosterone therapy in men with DM
Initial Evaluation of Hypogonadism in Men with DM

- At least two blood samples for calculated free testosterone (total and SHBG) drawn before 10 AM
- Baseline FSH, LH, Prolactin
- Safety data on CBC, PSA, DRE
- DEXA scan
- Most common etiology of the hypogonadism is centrally mediated. MRI should not be done unless serum T <150 ng/dl or other suspicions of a pituitary lesion
Sexual Dysfunction is Correlated to Poor Glucose Control

Corona, J Sexual Med 2012:99 (6); 1669-1680.
Parallel Decline in TT and FT Levels With Increasing BMI in Men


BMI, body mass index; FT, free testosterone; TT, total testosterone.

aP<.05, obese vs control.
bP<.01, obese vs control.
Endogenous Hormones Based on Risk Factors for Metabolic Syndrome

Risk Factors:
- Abdominal obesity
- Triglycerides
- HDL
- Fasting glucose
- BP

Lower Serum Total Testosterone in Men with MetS vs. Controls

Corona J Sex Med 2011;8:272-83
Low Testosterone is Associated with DM in Men

Ding, JAMA. 2006;295(11):1288-1299
Low Bio and Free T are Correlated to Insulin Resistance (HOMA-IR)

Low TT Levels Predict Development of Metabolic Syndrome and Diabetes

- Population-based cohort study (N=702): 11-y follow-up

Odds Ratio of having DM Increases with Lower T and SHBG and Lower E2

Multi Ethnic Study of Atherosclerosis
N=3156

Colangelo, Diabetes Care 2009:32(6);1049-51
Low Total T and SHBG are Correlated to Insulin Resistance (HOMA-IR)

Tsai E C et al. Dia Care 2004;27:861-868
Elevated SHBG Protects against Diabetes

Source
Men
Haffner et al, 1996
Stellato et al, 2000
Laaksonen et al, 2004
Random-Effects Pooled

Women
Lindstedt et al, 1991
Haffner et al, 1993
Random-Effects Pooled

Relative Risk (95% CI)

Ding, JAMA 2006;295(11):1288-1299
Low SHBG and Insulin Resistance: Cause or effect?

High caloric diet

Visceral adiposity

FAT

Circulating SHBG

Hepatic glucose production

Genetic variability in SHBG

+ Impaired beta-cell function

Type 2 Diabetes

Peters, Diabetes. 2010 December; 59(12): 3167–3173
Summary of Serum T in MetS and Diabetes

- Low serum testosterone vary from 20 to 64% depending on the population and whether total or free testosterone is used.
- This relationship persists even after adjustment for BMI, ethnicity, age and waist circumference.
- Still a strong confounder with obesity.
Outline

• General background
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• Effects of testosterone therapy in men with DM
How Low T Cause DM?

- Directly - Androgens inhibits glucose transport
  - Homologies between the GLUT1 receptor with the ligand-binding domain of the androgen receptor.
  - T inhibits glucose exit from erythrocytes via an external glucose-binding site of the GLUT1 receptor in vitro resulting in reduced insulin sensitivity

- Indirectly through changes in adipocytety
  - T normally promotes the pluripotent stem cell into myocytes, T deficiency results in adipocyte proliferation

Rosen & MacDougald 2006; Christodoulides et al. 2006, 2009
How Does DM Cause Low T?

- Biochemical - decreased SHBG levels
- Physiologic - suppression of gonadotrophin release
- Inflammatory - cytokine-mediated inhibition of testicular steroid production
- Enzymatic - increased aromatase activity leading to relative estrogen excess.
  - Often 2-fold higher
  - Reduced spermatogenesis
Low T Causes Excess Adipocytes and Inflammation Causes Low T

Saad, Curr Diabetes Rev 2013;8:131-143
Vicious Circle: Bidirectionality of Low Testosterone and Obesity

Decreased muscle mass
Increased fat mass

Low testosterone levels

Visceral obesity
Insulin resistance

Increased aromatase
Increased estradiol
Increased inflammatory factors

Outline

• General background
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Effect of Roux-en-Y gastric bypass on testosterone

Free Testosterone Increases with Weight Loss

Parenteral Testosterone Improves Body Composition in Elderly Men

Testosterone Therapy: Effect on Metabolic Syndrome Parameters

Body Weight, kg

Waist Circumference, cm

Testosterone Undecanoate Therapy, mo

0 3 6 9 12

±7.9 ±8.1 ±7.5 ±8.2 ±7.3

±11 ±13 ±11 ±11 ±7

\(^aP<.05\) vs baseline.

Reduced Insulin Resistance after Testosterone Therapy in Diabetics

HOMA Index

$\text{HOMA-IR} = \text{fasting insulin} \times \text{fasting glucose}/22.5$; HOMA was not measured in patients treated with insulin.

CAD, coronary artery disease; HOMA, homeostatic model assessment; HOMA-IR, homeostatic model assessment of insulin resistance; IR, insulin resistance.

Reproduced from Cornoldi A et al. *Int J Cardiol.* 2010;142(1):50-55.
Anthropometric Changes in a Double-Blind, Placebo-controlled Moscow Study in 184 Men with Metabolic Syndrome.

Δ Body mass index (kg/m²)

Δ weight (kg)

Δ waist (cm)

18 wk vs. baseline
30 wk vs. baseline

P<0.001

P<0.001

P<0.001

Kalinchenko SYClin Endocrinol (Oxf) 2010;73:602–12
Improved Glycemic Control in Hypogonadal Men Treated With Testosterone Therapy

Patients Treated With Testosterone Therapy

Patients With Metabolic Syndrome

Patients With Type 2 Diabetes

Mean (95% CI) Change From Baseline in HOMA-IR, %

<table>
<thead>
<tr>
<th>Phase</th>
<th>Group</th>
<th>Baseline</th>
<th>6 mo</th>
<th>12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>0</td>
<td>-5</td>
<td>-10</td>
</tr>
<tr>
<td></td>
<td>2% Testosterone gel</td>
<td>0</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

Phase 1:
- Placebo: n=82
- 2% Testosterone gel: n=80

Phase 2:
- Placebo: n=82
- 2% Testosterone gel: n=80

\[ aP=.069. \]
\[ bP=.054. \]

CI, confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance.

Mechanisms to Explain the Improvement of DM with TRT

- Decreased visceral adiposity
- Reduced anti-inflammatory mechanisms.
  decrease visceral adiposity
- Positively associated with VAT expression of GLUT4, and ADPN – two markers of insulin sensitivity
Weight Change (% from Baseline) in Men Treated with Testosterone Undeconoate

- 13.57%

*p<0.0001 vs baseline

Saad F et al. Obes, published online March 20, 2013
Fasting Glucose (mmol/L) in 71 Obese Hypogonadal Men with Type 2 DM treated with TU up to 60 mo

Saad F et al. Obes, published online March 20, 2013
HbA1c (%) in 71 Obese Hypogonadal Men with Type 2 Diabetes Treated with TU up to 60 mo

*p<0.0001 vs baseline # p<0.0001 vs previous year

Saad F et al. Obesity, published online March 20, 2013
Clinical Therapeutics: Target Sites

- Activation of NOS (Nitric Oxide Synthase) leads to the production of Nitric Oxide (NO), which activates the enzyme Guanylyl Cyclase, leading to the formation of cGMP (cyclic Guanosine Monophosphate).
- cGMP activates Protein Kinase G (PKG).
- PKG phosphorylates proteins, which can lead to changes in cell function.
- Inhibition of PDE-5 (Phosphodiesterase 5) prevents the breakdown of cGMP, maintaining its activity.
- Lowering of calcium ions (Ca^{2+}) facilitates relaxation (RELAXATION).

The diagram illustrates the process involving neurons or endothelium leading to smooth muscle relaxation through the cascade of events involving NO, cGMP, PKG, and PDE-5.
Erectile Dysfunction and Testosterone Deficiency: Castration Effects in the Penis

• Structural
  ♦ Vascular smooth muscle cell atrophy
  ♦ Subtunical adipocyte deposition
  ♦ Loss of elastic fibers
  ♦ Increased collagen deposition

• Functional
  ♦ Decreased nitric oxide synthase function
  ♦ Decreased phosphodiesterase type 5 function
Testosterone Undecanoate Improves Sexual Function and Quality-of-Life Parameters vs. Placebo in Men with Type 2 DM

Hackett, J Sexual Med 2013;10:6;1612-1627,
Benefits were greater in less obese men and those aged over 60, probably due to lower therapeutic levels of testosterone being attained.

Improvements were seen within 6 weeks and continued to improve beyond 12–18 months.

Depression reduced the response to testosterone in terms of sexual function and AMS, but modest improvement in depression was seen with testosterone therapy beyond 12 months.

Erectile Function and Testosterone Actions: Hormone Regulation in the Penis

• Structural
  ♦ Erectile tissue integrity

• Functional
  ♦ Normal nitric oxide synthase function
  ♦ Normal phosphodiesterase type 5 function
Androgen Effect on Erectile Responses to PDE5 Inhibitors: Clinical Trials

Prospective open label study of 48 hypogonadal men with ED administered 1% 5gm T-gel for 6 months

- 31 of 48 men had improved erectile function scores using testosterone supplements alone
- 17 of 48 men who did not improve erectile function scores using testosterone supplements alone did improve after additional treatment of 100mg sildenafil for 3 months

Greenstein A et al. J Urol 173:530-2, 2005
Oral PDE5 Inhibitors and Hormonal Treatments for Erectile Dysfunction: A Systematic Review

- Meta-analysis of randomized, controlled trials\(^1\)
  - Evidence was insufficient to determine whether combined therapy was more effective (n=3 RCT)

- Limitations of reported trials\(^2\)
  - Many were short-term (≤ 12 weeks)
  - Many contained limited numbers of patients
  - Many contained patients who were not truly hypogonadal

Summary I

- In corpus cavernosum of animal models and humans, PDE5 function is androgen dependent.
- The effect has in vivo significance and is pertinent for penile responsiveness to PDE5 inhibitors and the treatment of erectile dysfunction.
- Despite limited evidence, recommendations are supported to treat testosterone deficiency initially, and if the response is inadequate, add a PDE5 inhibitor.
Conclusion

• In epidemiologic-type studies, men with diabetes/metabolic syndrome have lower serum T and free T by 25-50% compared to controls

• Hypogonadism contributes to both the result and cause of DM/metabolic syndrome likely mediated through the metabolism of visceral fat pathology and inflammation

• Clinicians should consider weight loss first, followed by testosterone therapy to affect overall cardiovascular health, parameters of metabolic syndrome, morbidity, and mortality

• Could testosterone be a measure of more fitness less fat?