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

Adrian Dobs, M.D., M.H.S.

Professor of Medicine and Oncology

The Johns Hopkins University School of Medicine



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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



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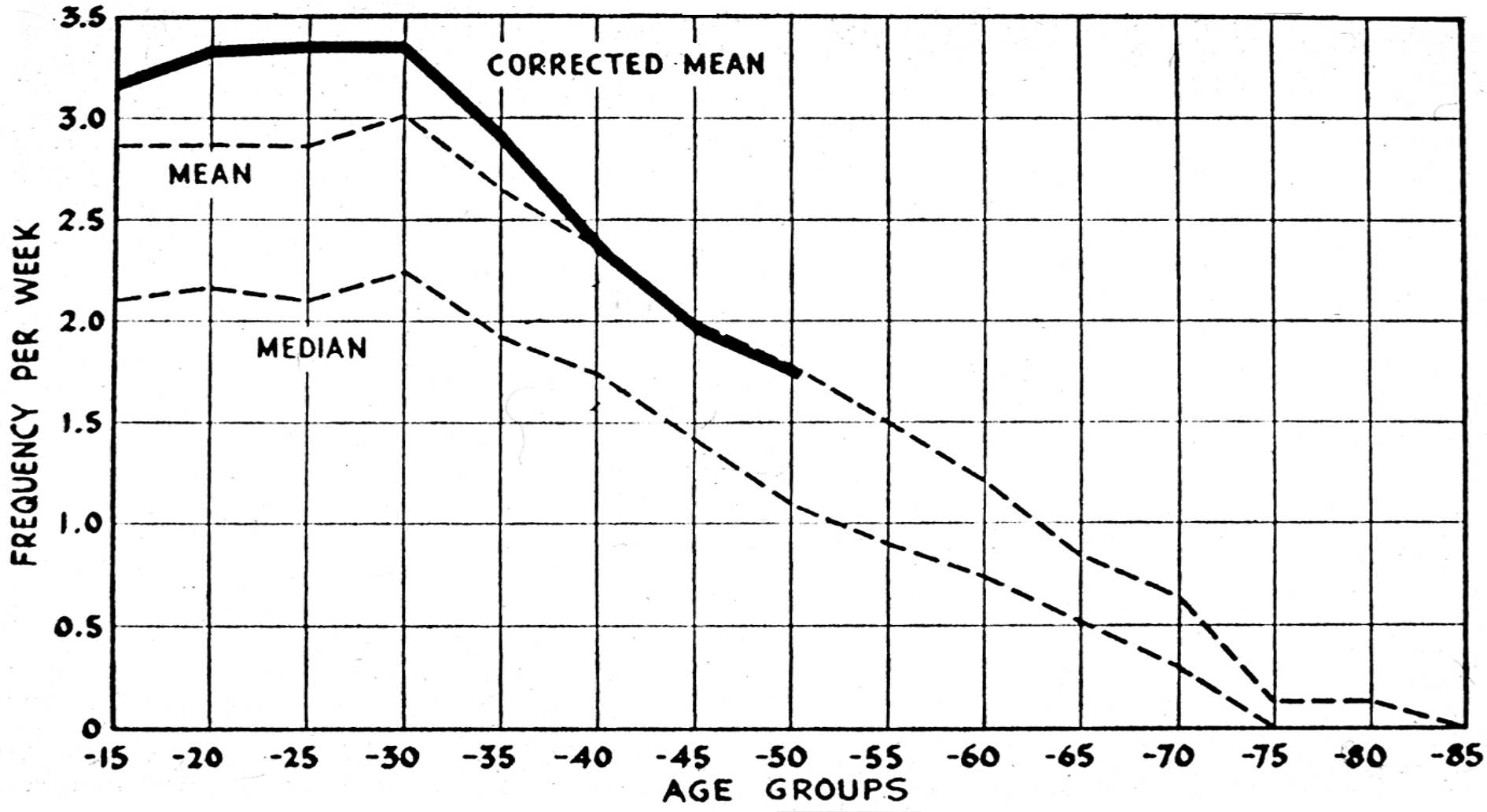
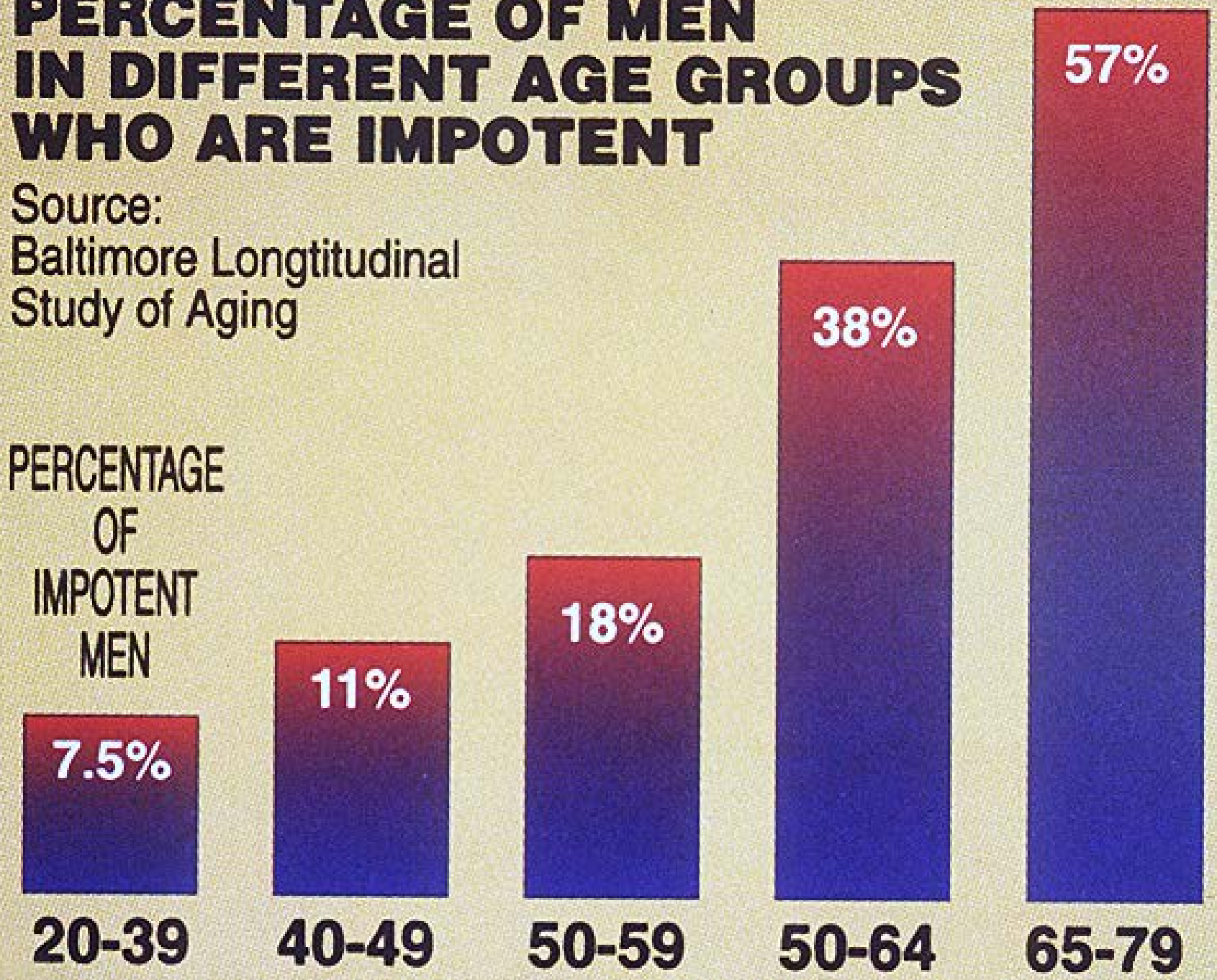
# Frequency of Sexual Relationships based on Age

(Kinsey, 1963)



# PERCENTAGE OF MEN IN DIFFERENT AGE GROUPS WHO ARE IMPOTENT

Source:
Baltimore Longtitudinal
Study of Aging



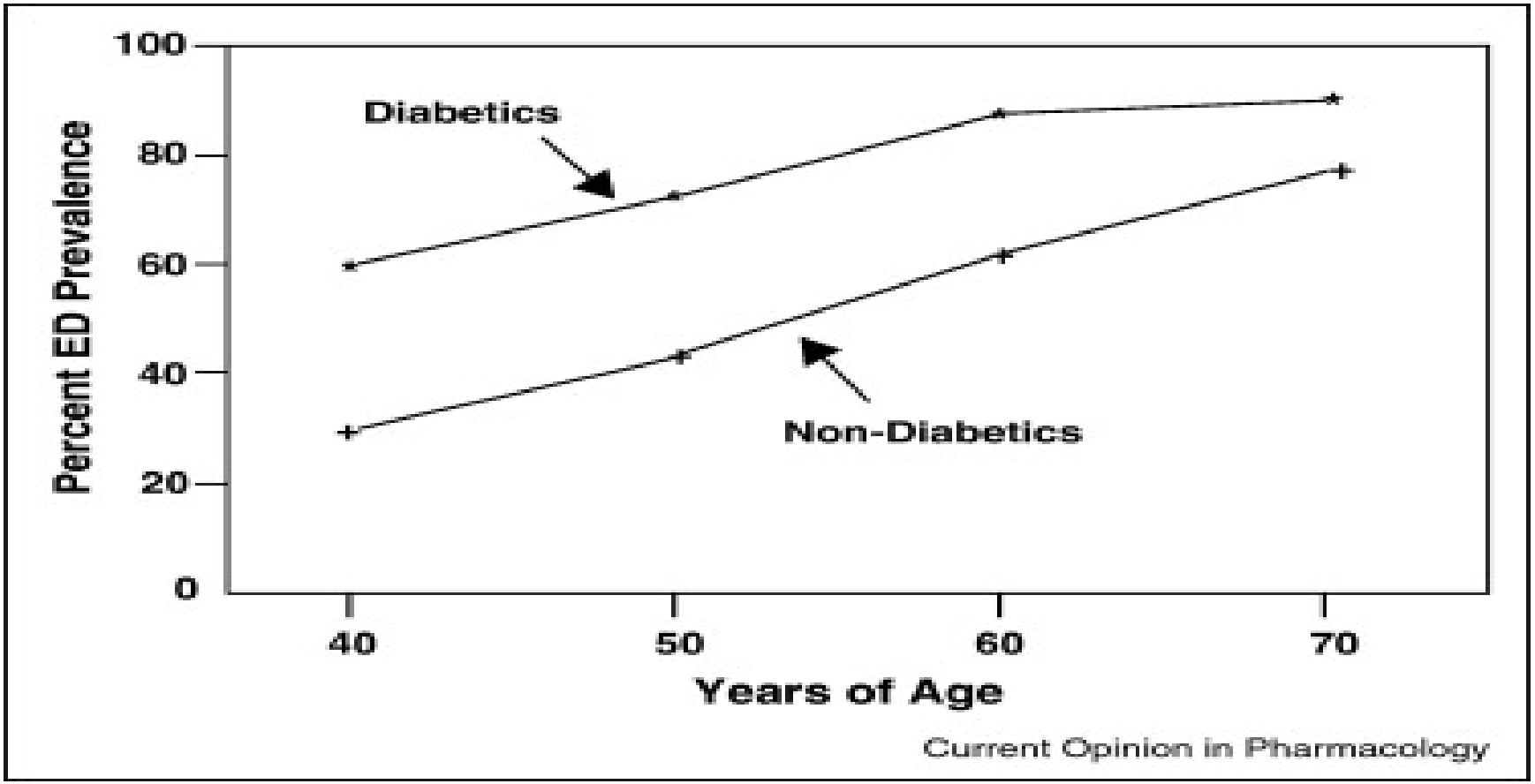
# Questions to Evaluate Sexual Function in Men and Women

- **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

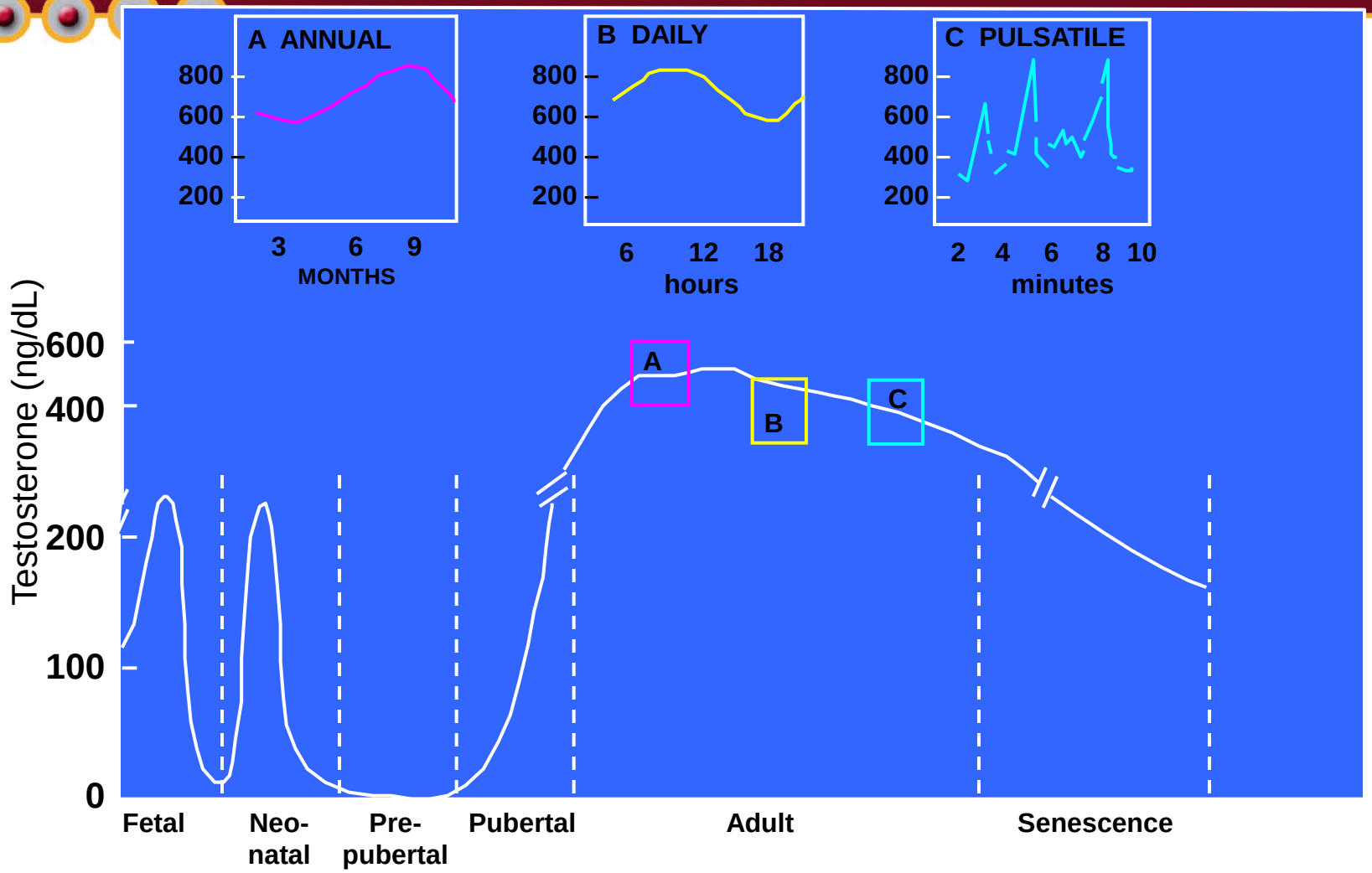
- **Systematic diseases:**
  - Atherosclerosis
  - Diabetes Mellitus
  - Renal Failure
  - Hepatic failure
- **Neurogenic diseases:**
  - Alzheimer's disease
- **Penile disorders:**
  - Peyronie's disease
- **Psychiatric disorders:**
  - Depression
  - Performance Anxiety
- **Endocrine disorders:**
  - Hyperthyroidism
  - Hypothyroidism
  - Hypogonadism
  - Hyperprolactinemia

# Increased frequency and Lower age of onset of erectile dysfunction in type II DM vs non-diabetics.



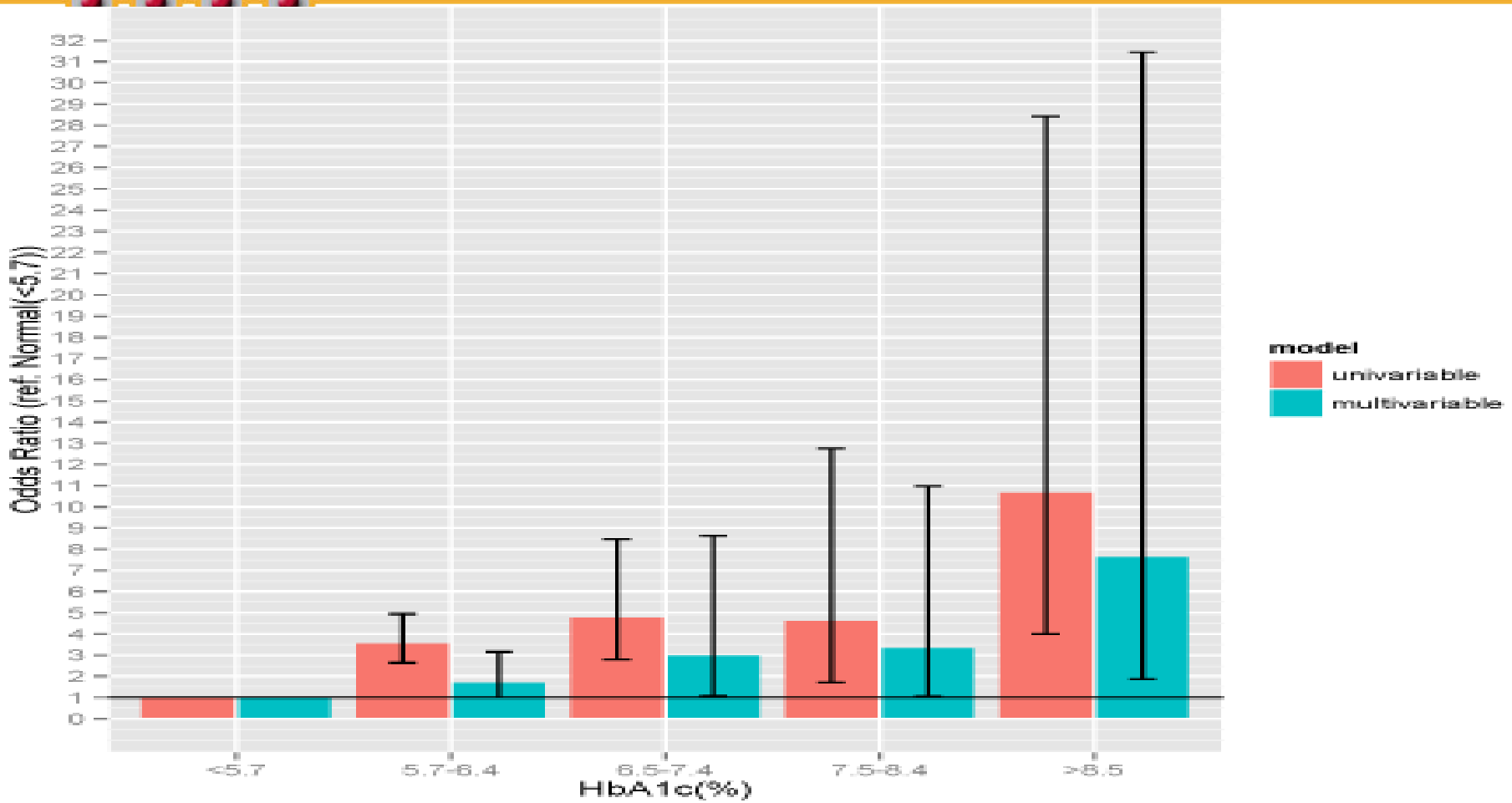

Francis and Corbin, Current Opinion in Pharmacology Volume 11, Issue 6 2011 683 - 688

# Plasma Testosterone Levels During the Life Cycle in Men




Ewing LL, et al. *Int Rev Physiology*. 1980;22:41-115.

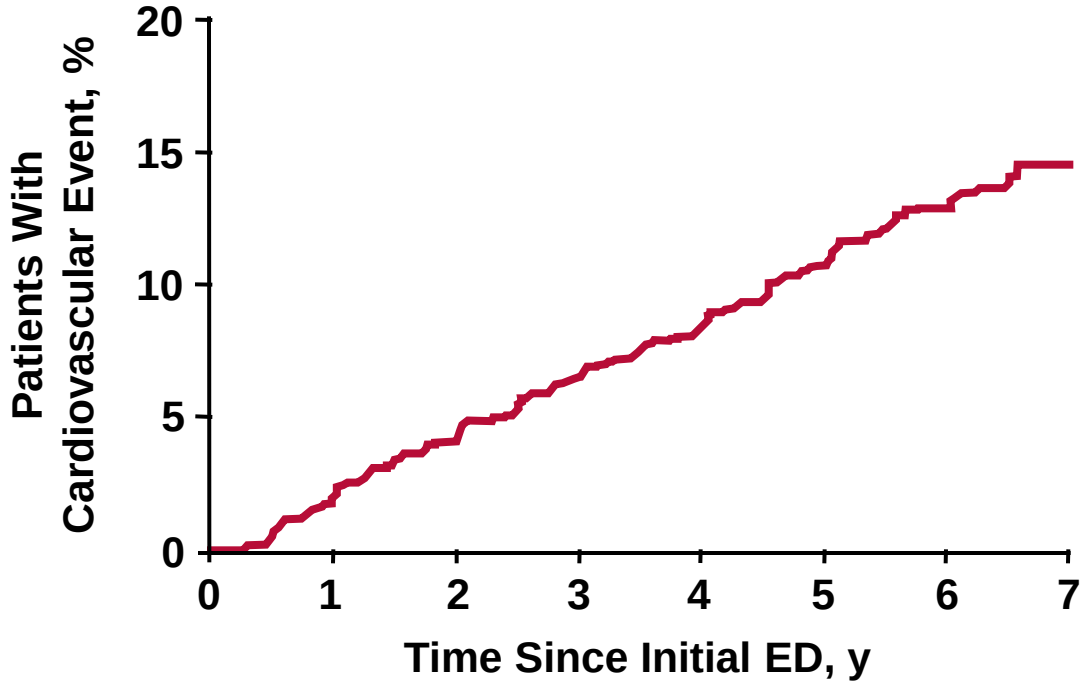
# Increased Risk of Erectile Dysfunction with Worsening Glycemic Control




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%

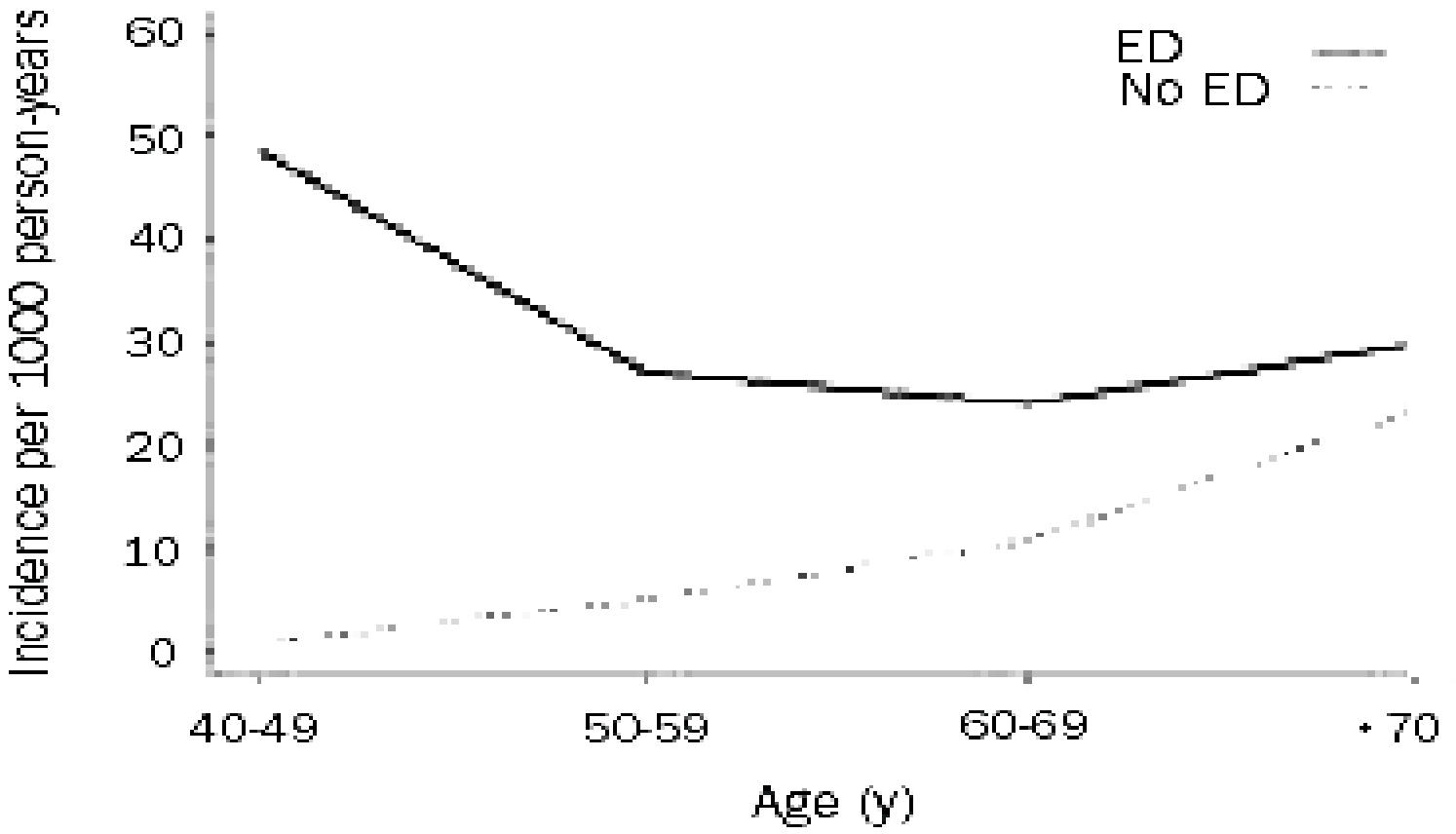



- Of 8063 men without CVD at study entry, 3816 (mean age, 62 y) had ED
- Among 4247 men without ED at study entry, 2420 reported incident ED after 5 y

CVD, cardiovascular disease; ED, erectile dysfunction.

Reproduced from Thompson IM et al. *JAMA*. 2005;294(23):2996-3002.

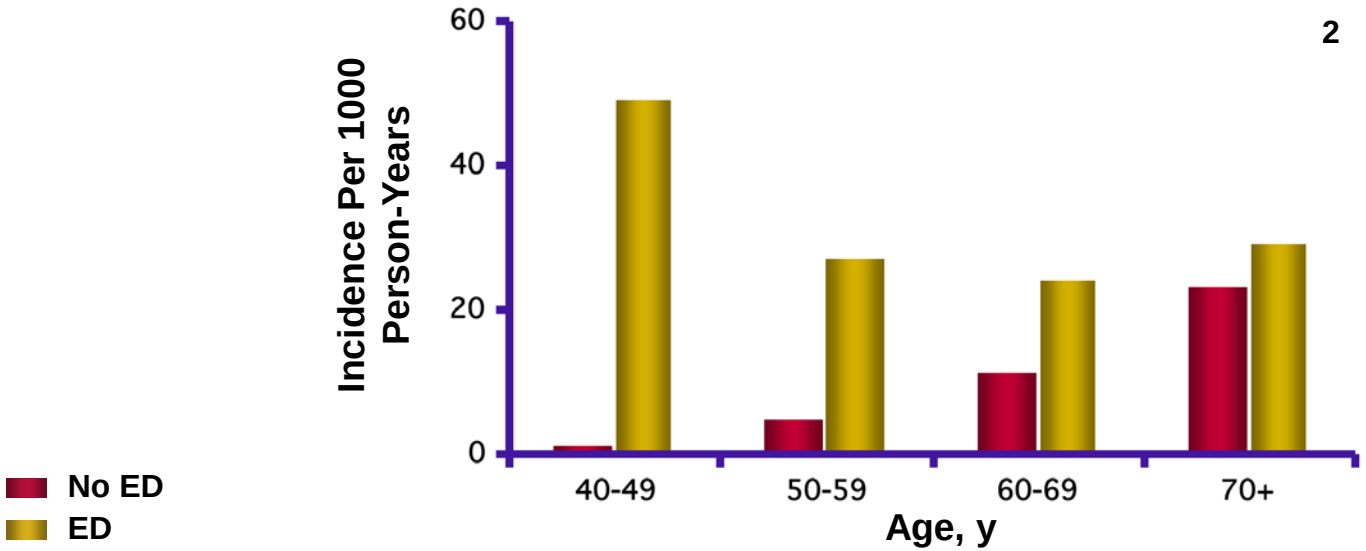
# ED Predicts Coronary Events: 10-Year Follow-up




Inman BA et al. *Mayo Clin Proc.* 2009;84(2):108-113.

# ED Predicts Coronary Events: 10-Year Follow-up

- 2115 men from Olmstead County Study of Urinary Symptoms and Health Status Among Men[1]
  - 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[1]
- ED in younger men related to marked increase in risk of cardiac events[1]
- ED in older men of little prognostic importance[1]




2

CAD, coronary artery disease; ED, erectile dysfunction.

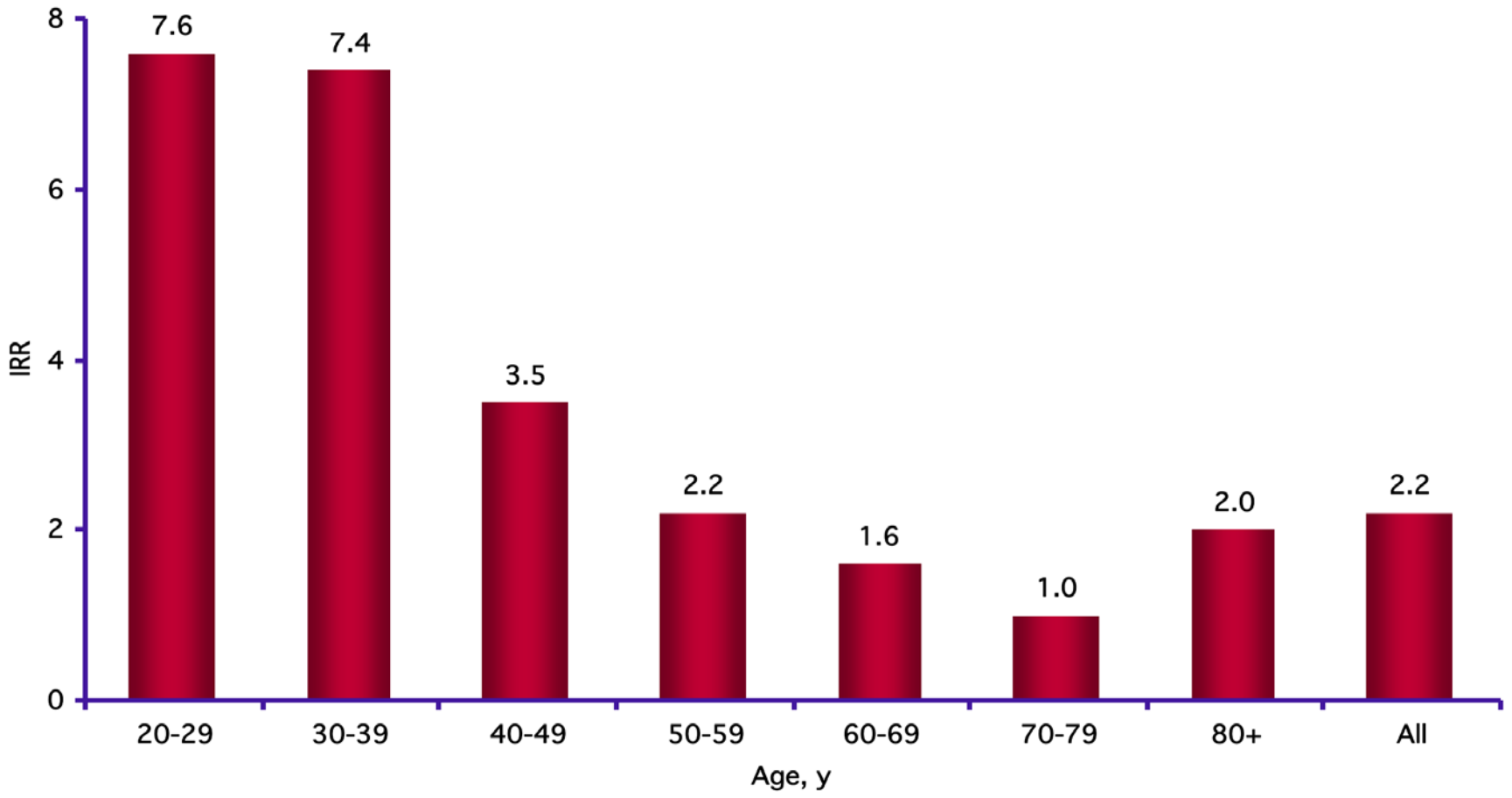
1. Inman BA et al. *Mayo Clin Proc.* 2009;84(2):108-113. 2. Reproduced from Miner MM. *J Androl.* 2011;32(2):125-134.

# 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**

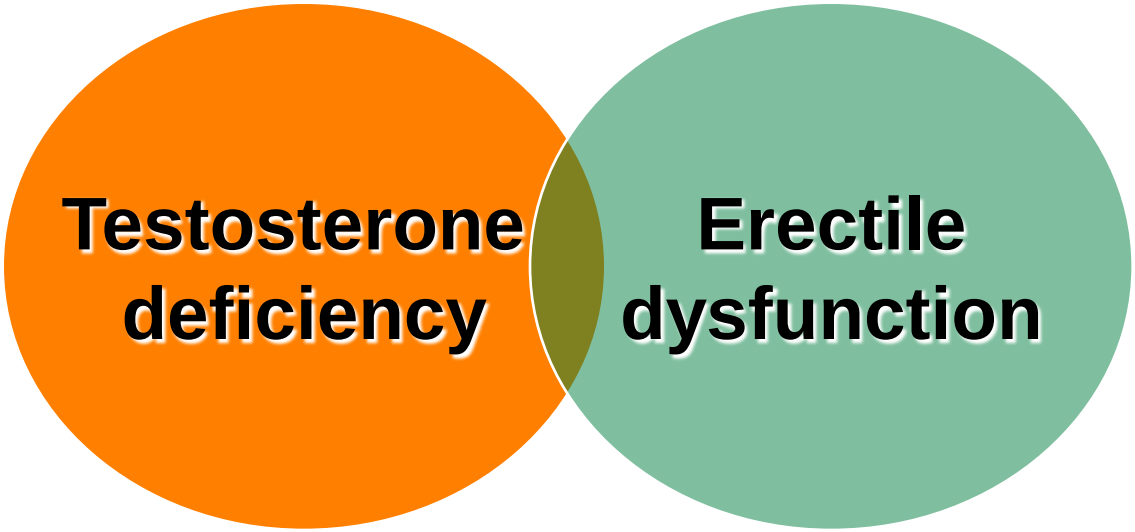
Chew KK et al. *J Sex Med*. 2010;7(1 Pt 1):192-202.

# Stronger Relationship Between ED and CVD in Young Men




Chew KK et al. *J Sex Med*. 2010;7(1 Pt 1):192-202.

# ED and testosterone deficiency are independently distributed disorders



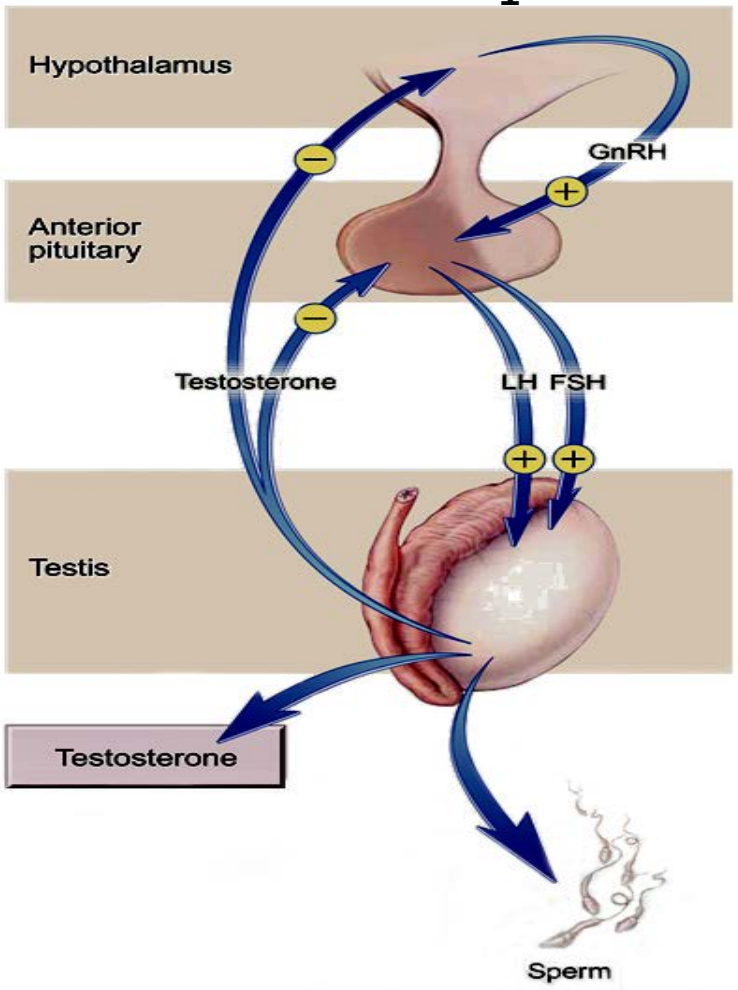

- **Between 2.1% and 21% of men with ED have low levels of serum testosterone, depending on the test used to measure testosterone**

Korenman SG, et al. J Clin Endocrinol Metab. 1990;71:963-9.
Buvat J, Lemaire A. J Urol. 1997;158:1764-7.
Nehra A. Mayo Clin Proc. 2000;75 Suppl:S40-5.
Shabsigh R. Int J Impot Res. 2003;15 Suppl 4:S9-13.

ED = erectile dysfunction.

# Production and Regulation of Testosterone

1

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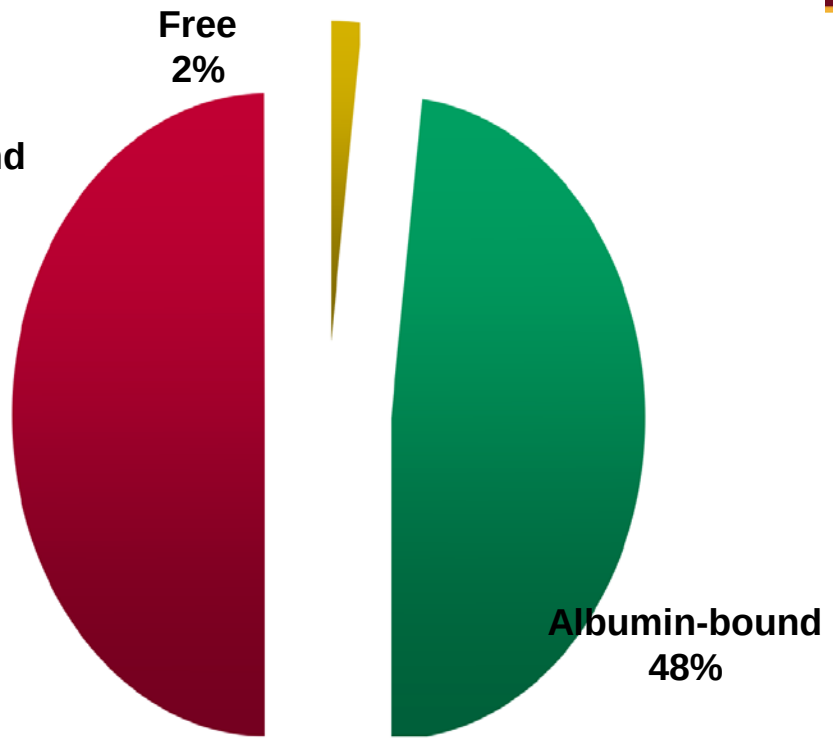



**Only 2% is free testosterone; 98% is bound**

1. Reproduced from Bagatell CJ, Bremner WJ. *N Engl J Med*. 1996;334(11):707-714. 2. Adapted from Braunstein GD. In: *Basic & Clinical Endocrinology.* 5th ed. Stamford, CT: Appleton & Lange; 1997:403-433.

# Types of Hypogonadism Include

| Primary (congenital or acquired) | Hypogonadotropic (congenital or acquired) |
|---|---|
| Testicular failure due to conditions such as<br>• Cryptorchidism<br>• Bilateral torsion<br>• Orchitis<br>• Vanishing testis syndrome<br>• Orchiectomy<br>• Klinefelter syndrome<br>• Chemotherapy<br>• Toxic damage from alcohol, heavy metals | • Idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency<br>• Pituitary-hypothalamic injury from tumors, trauma, or radiation |
| • **These men usually have**<br>– **Low serum testosterone concentrations**<br>– **Gonadotropins (FSH and LH) above the normal range** | • **These men have**<br>– **Low serum testosterone concentrations**<br>– **Gonadotropins in the normal or low range** |

# Challenges in Measuring Serum Total or Free Testosterone

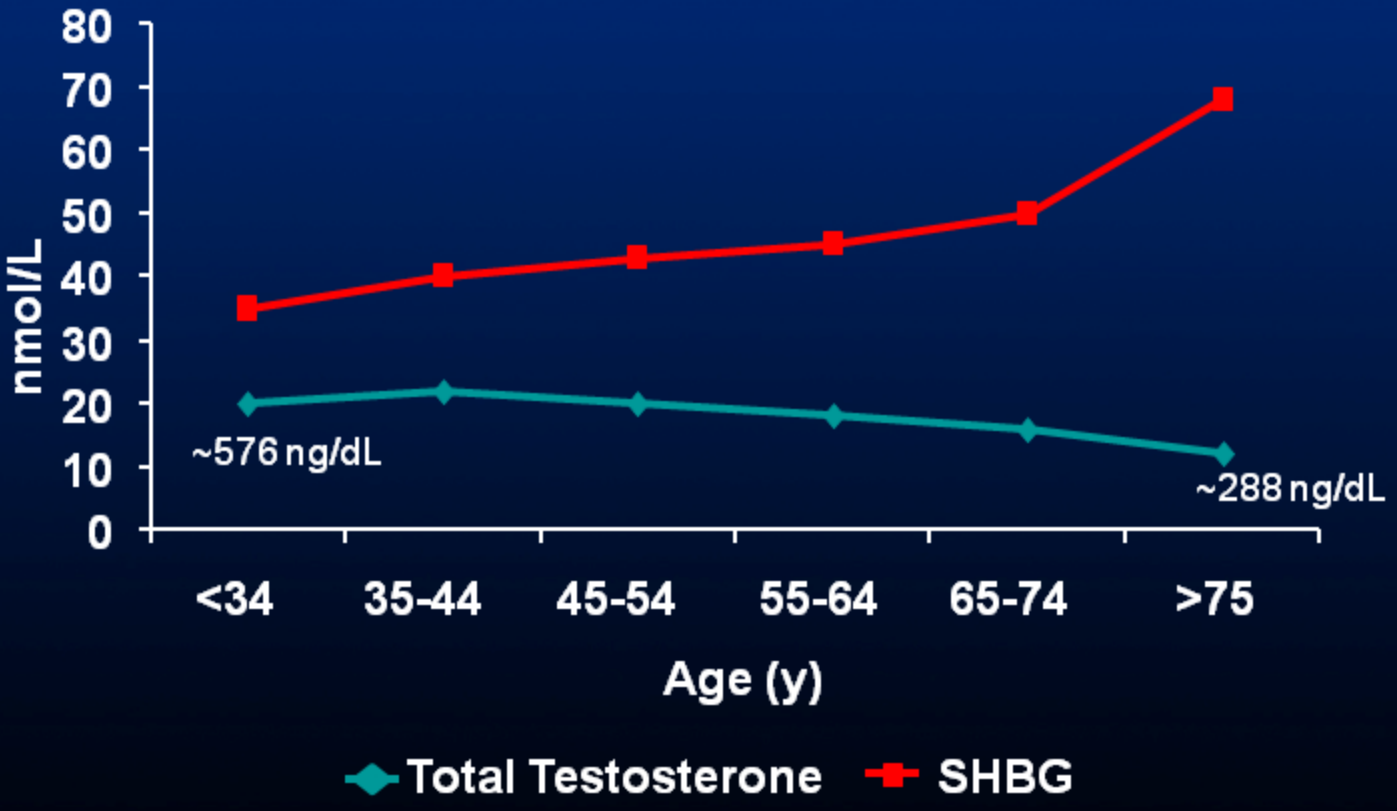
- **Variability in serum testosterone levels due to biology, circadian rhythms, and laboratory assays**
- **LC-MSMS represented the gold standard test in a study comparing different laboratory methods for measuring total testosterone**
- **Total testosterone less than 150 ng/dL had specificity >95%, 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 bioavaliable T**
  - **Aging**
  - **HIV, hepatitis**

# Male Hormonal Status

## Changes With Age as SHBG Increases

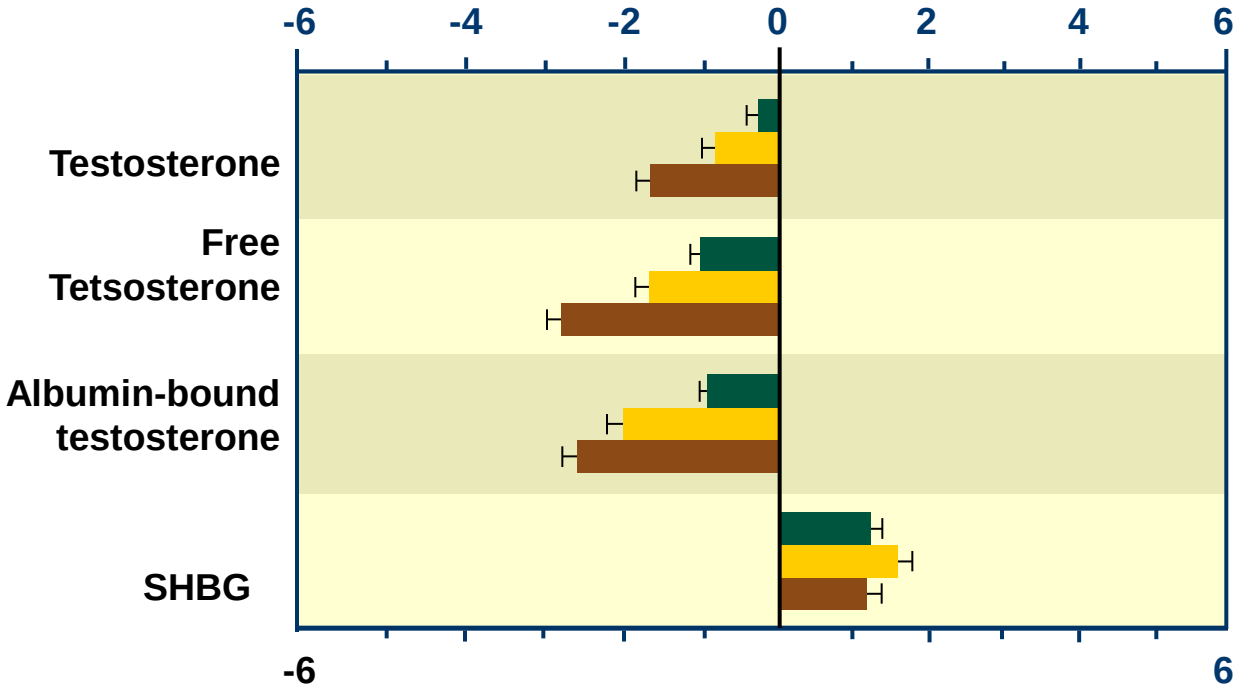



As SHBG increases with age, levels of free testosterone decrease

Gray A, et al. *J Clin Endocrinol Metab*. 1991;73:1016-1025.

# Effects of Aging on Hormone Levels

## *Massachusetts Male Aging Study (MMAS)*




Feldman HA et al. *J Clin Endocrinol Metab*. 2002;87(2):589-598.

# Hypogonadism Signs and Symptoms

**Endocrine Society guidelines[1]**

- **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 dysfunction[2]**

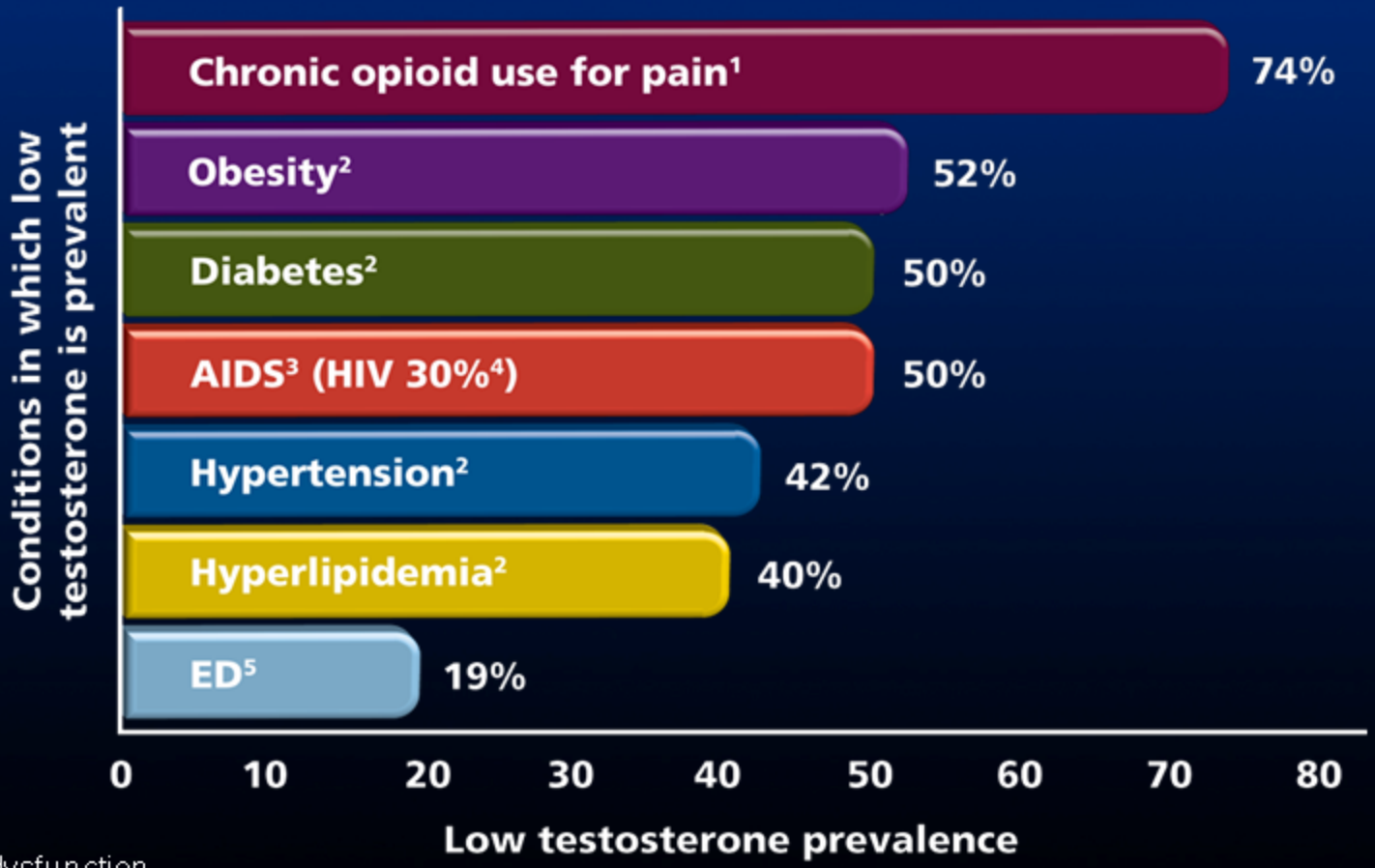
**Present in 2% of the 3300 men**

1. Bhasin S et al. *J Clin Endocrinol Metab.* 2010;95(6):2536-2559. 2. Wu FC et al. *N Engl J Med.* 2010;363(2):123-135.

# 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




ED = erectile dysfunction

1. Daniell HW. *J Pain*. 2002;3:377-384; 2. Mulligan T, et al. *Int J Clin Pract*. 2006;60:762-769; 3. Grinspoon S, et al. *Ann Intern Med*. 1998;129:18-26; 4. Dobs AS. *Baillière's Clin Endocrinol Metab*. 1998;12:379-390; 5. Bodie J, et al. *J Urol*. 2003;169:2262–2264.

# Endocrine Society Guidelines for Screening for Low T

- **Screening for low T is not recommended in all patients**

| Recommended Patients to Screen | NOT Recommended to Screen |
|---|---|
| • Type 2 diabetes mellitus<br>• Treatment with medications, including opioids and glucocorticoids<br>• HIV-associated weight loss<br>• End-stage renal disease and maintenance hemodialysis<br>• Moderate to severe chronic obstructive lung disease<br>• Sexual dysfunction or Infertility<br>• Osteoporosis or low trauma fracture<br>• Sellar mass<br>• Sexual dysfunction | • General population |

**Bhasin S et al. *J Clin Endocrinol Metab*. 2010;95:2536-2559.**



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# Outline

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- **Serum sex hormones in glucose intolerance, DM and metabolic syndrome**
- Mechanisms to explain reduced serum T levels
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# 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



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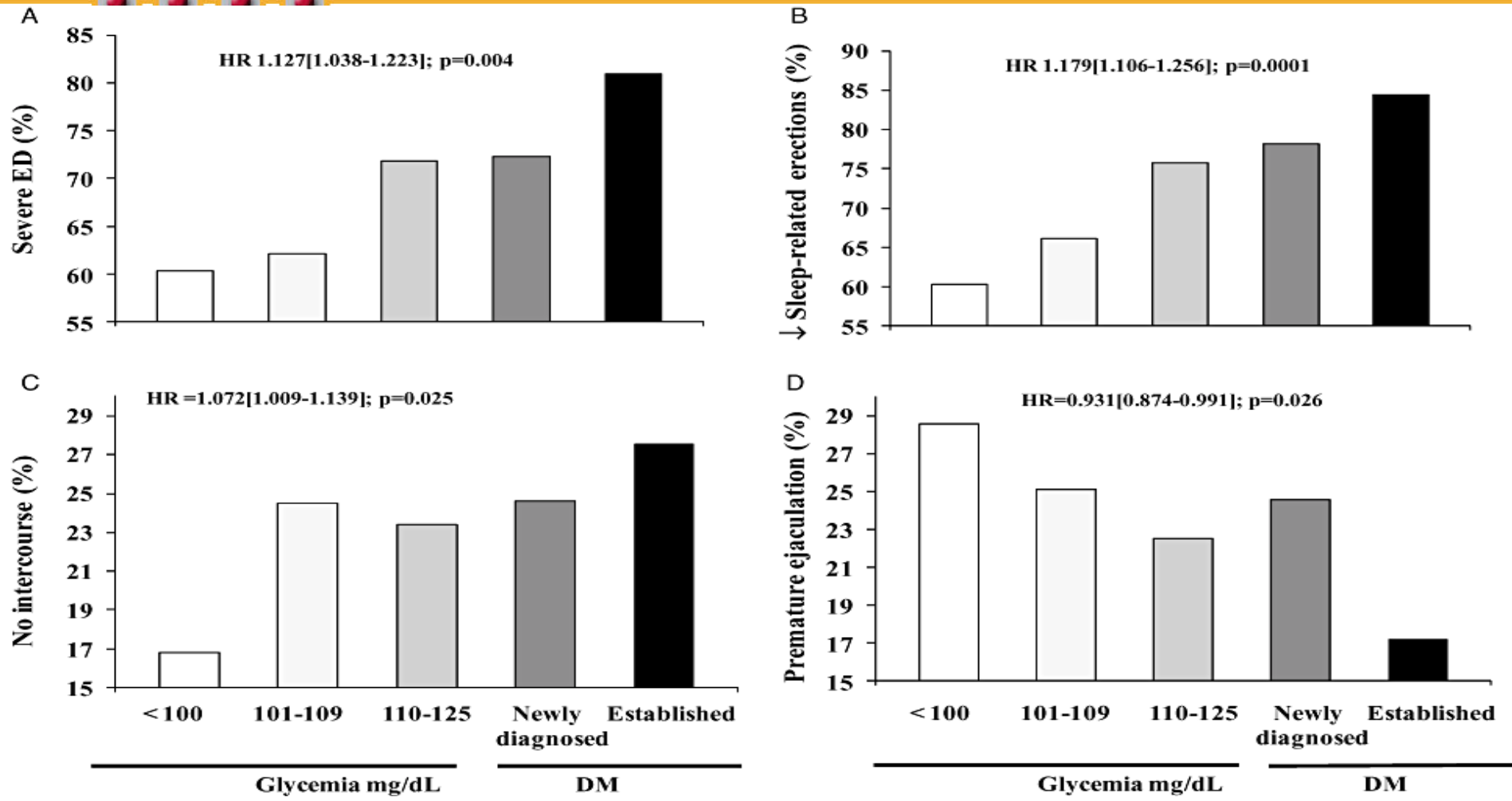
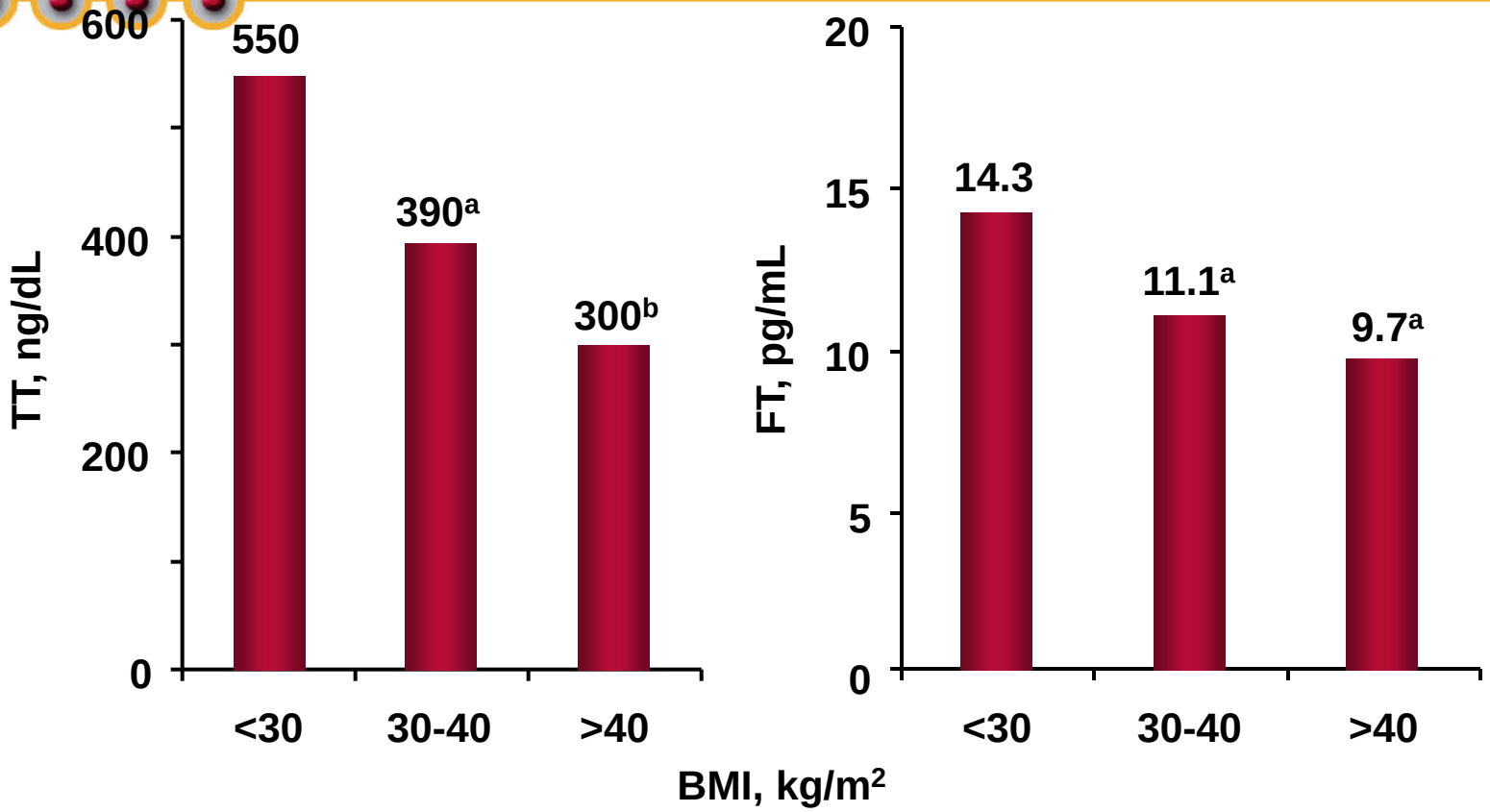
# Sexual Dysfunction is Correlated to Poor Glucose Control




Corona, J Sexual Med 2012:99 (6); 1669-1680,.

# Parallel Decline in TT and FT Levels With Increasing BMI in Men

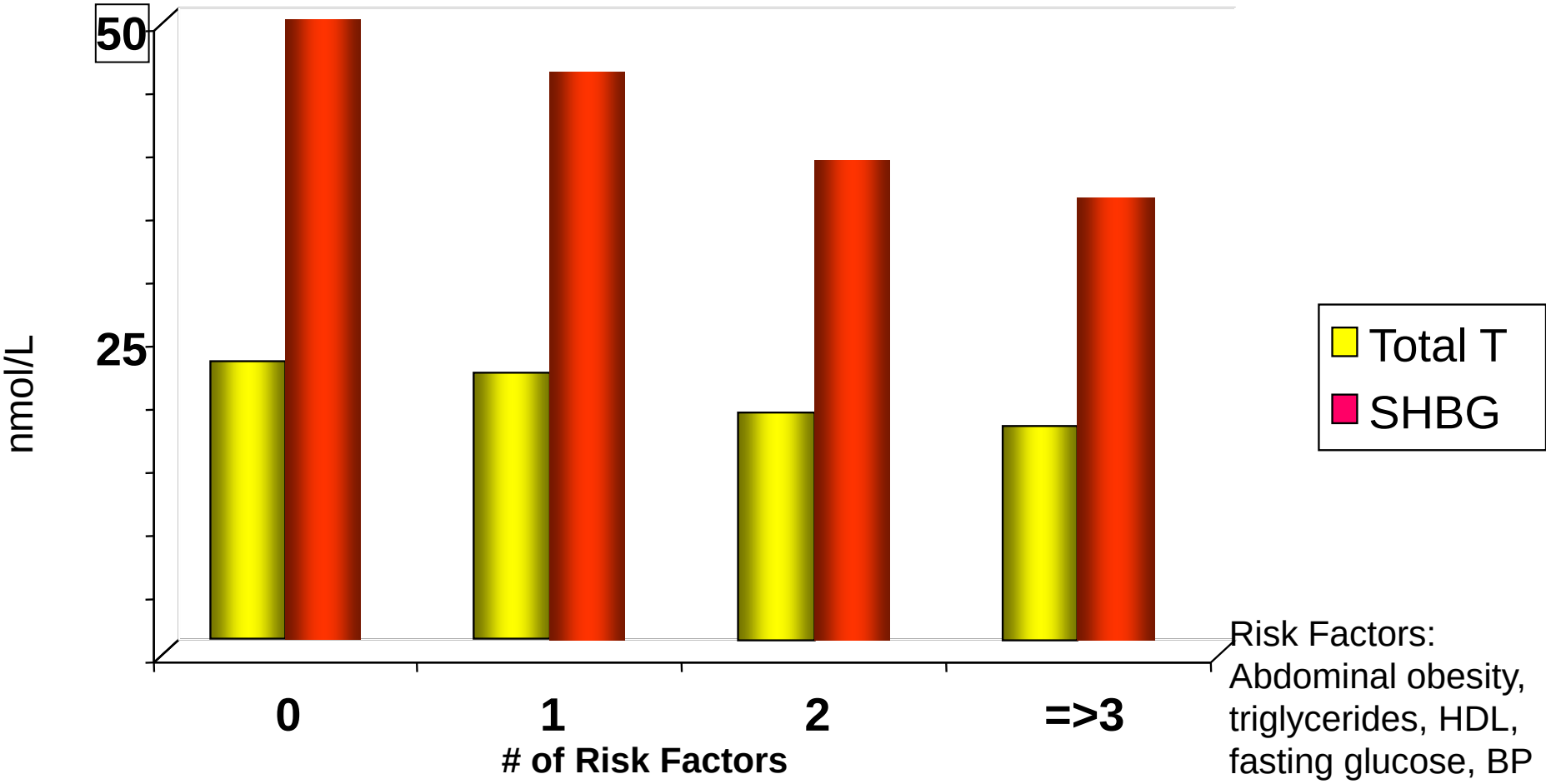



[a]*P*<.05, obese vs control.
[b]*P*<.01, obese vs control.

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

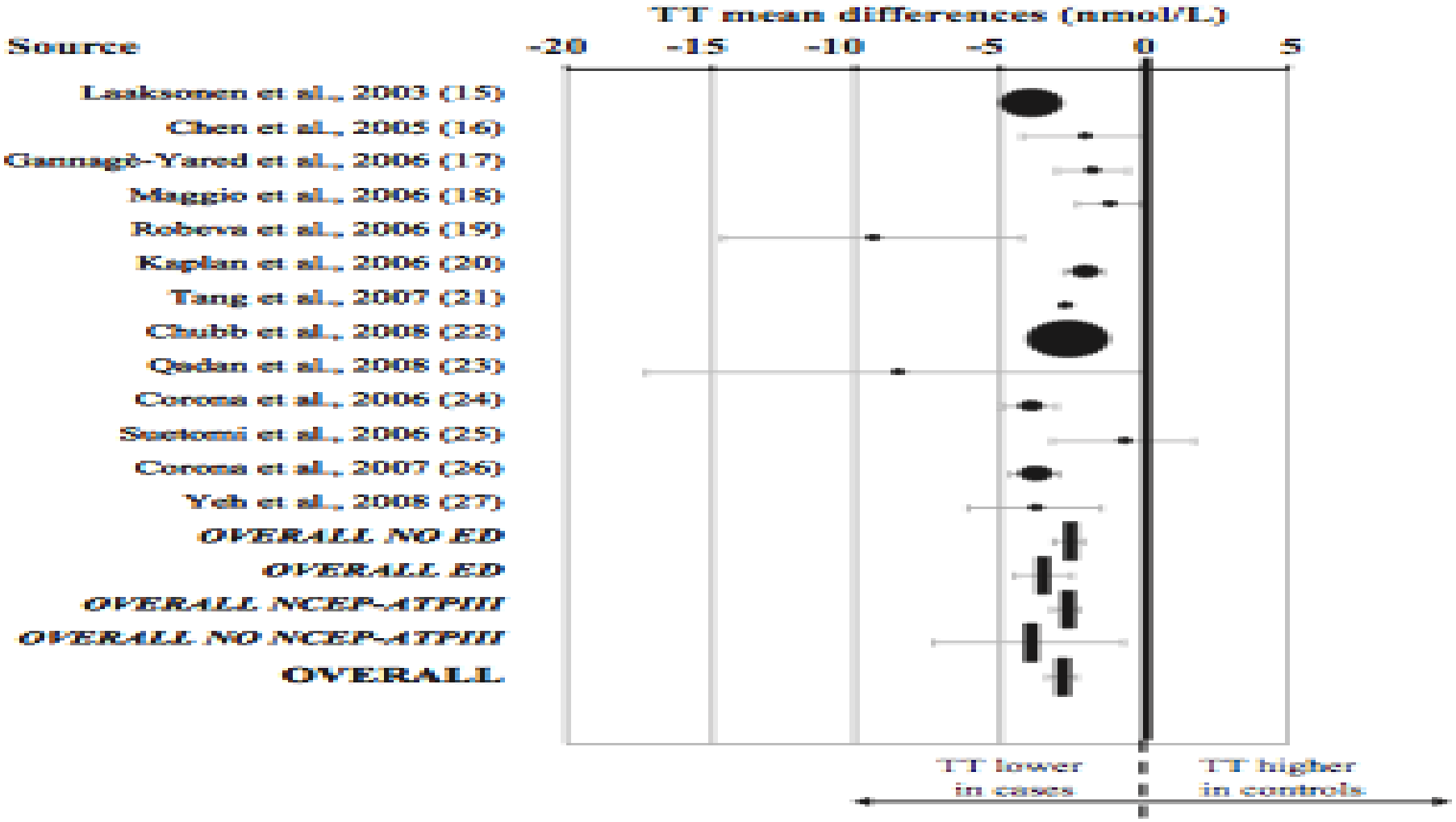
Isidori AM et al. *J Clin Endocrinol Metab.* 1999;84(10):3673-3680.

# Endogenous Hormones Based on Risk Factors for Metabolic Syndrome



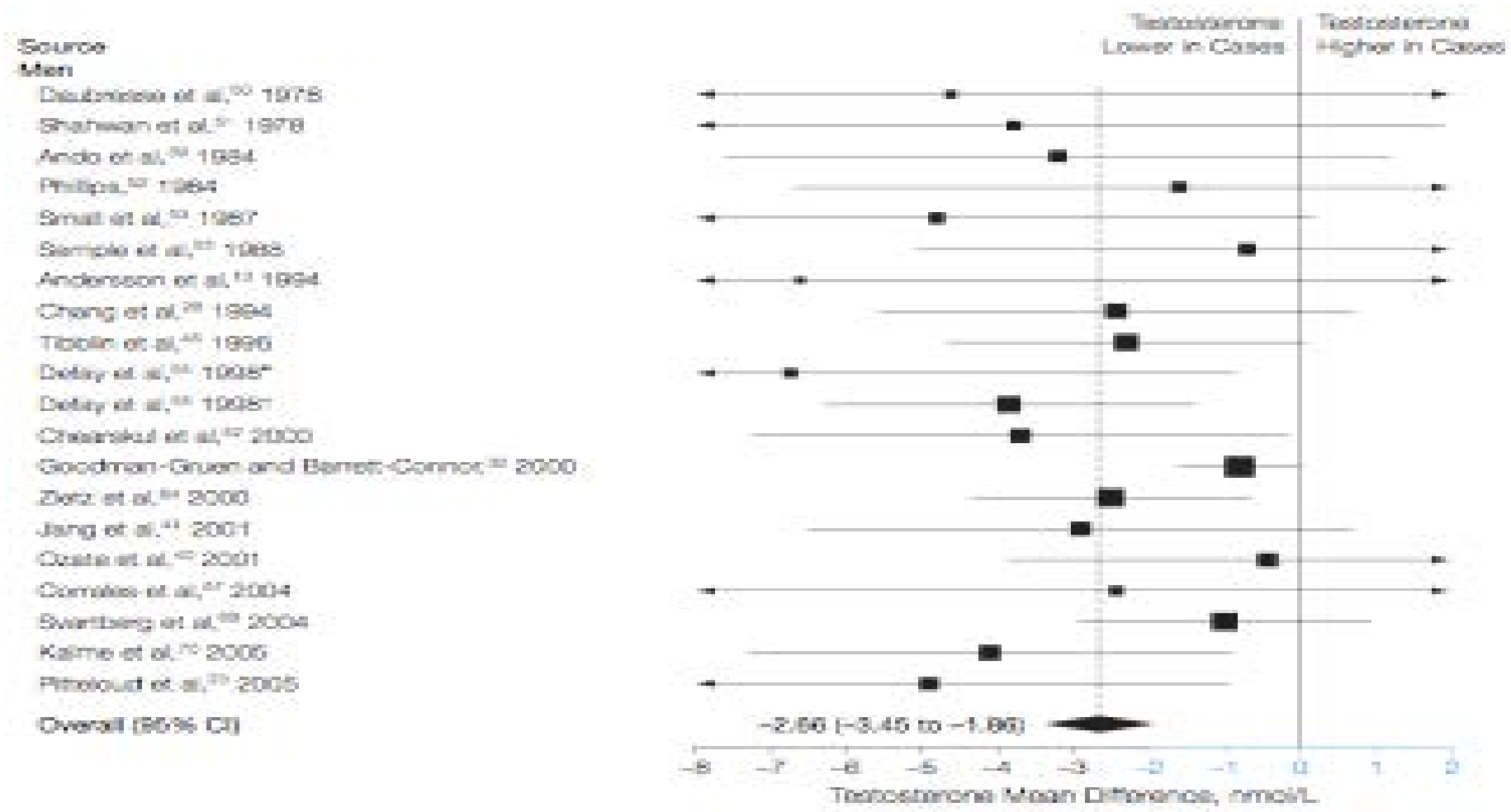

Muller, M. et al. *J Clin Endocrinol Metab* 2005; 90:2618-2623.

# Lower Serum Total Testosterone in Men with MetS vs. Controls



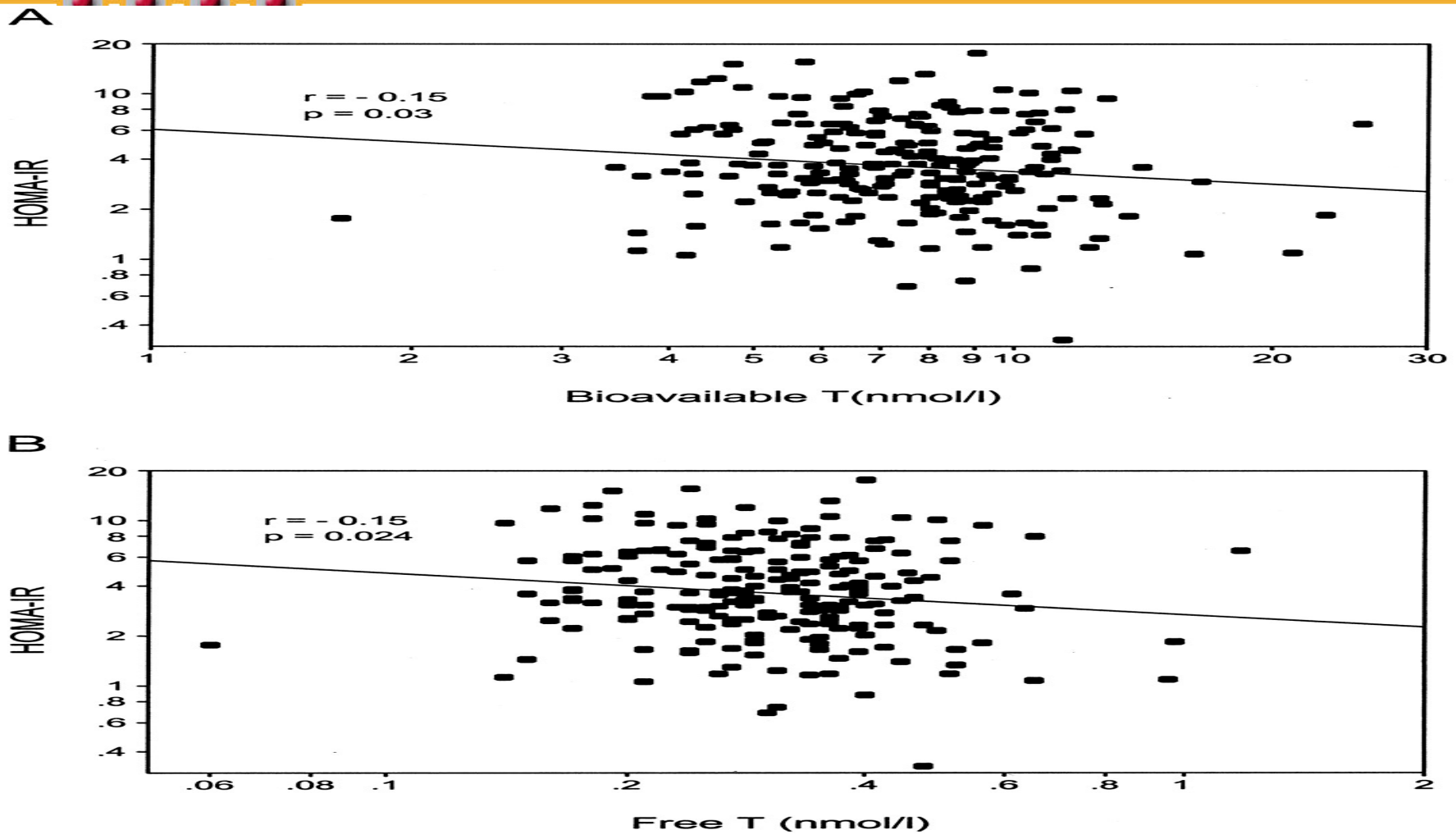

Corona J Sex Med 2011;8:272-83

# Low Testosterone is Associated with DM in Men




Ding, JAMA. 2006;295(11):1288-1299

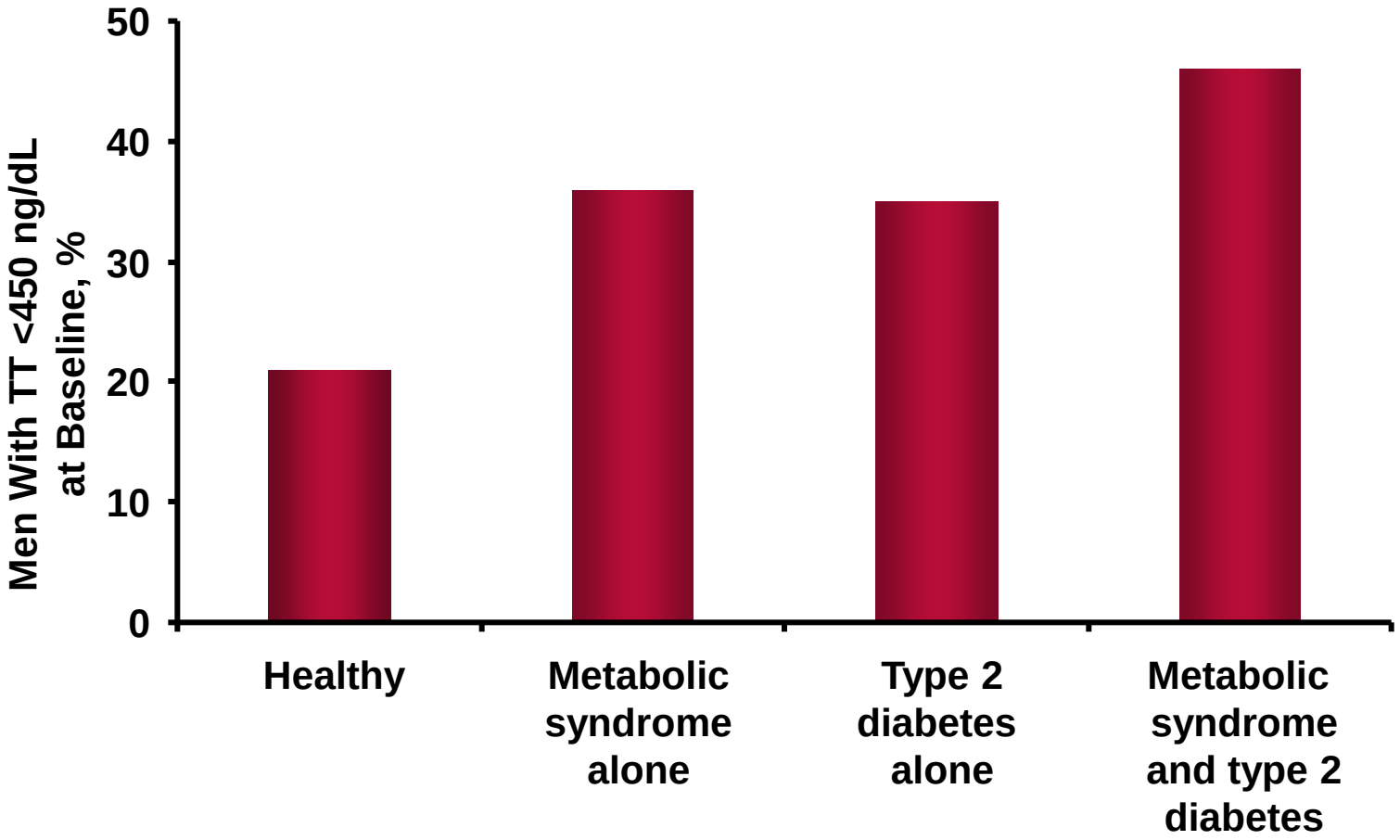
# Low Bio and Free T are Correlated to Insulin Resistance (HOMA-IR)




Tsai E C et al. Diabetes Care 2004;27:861-868

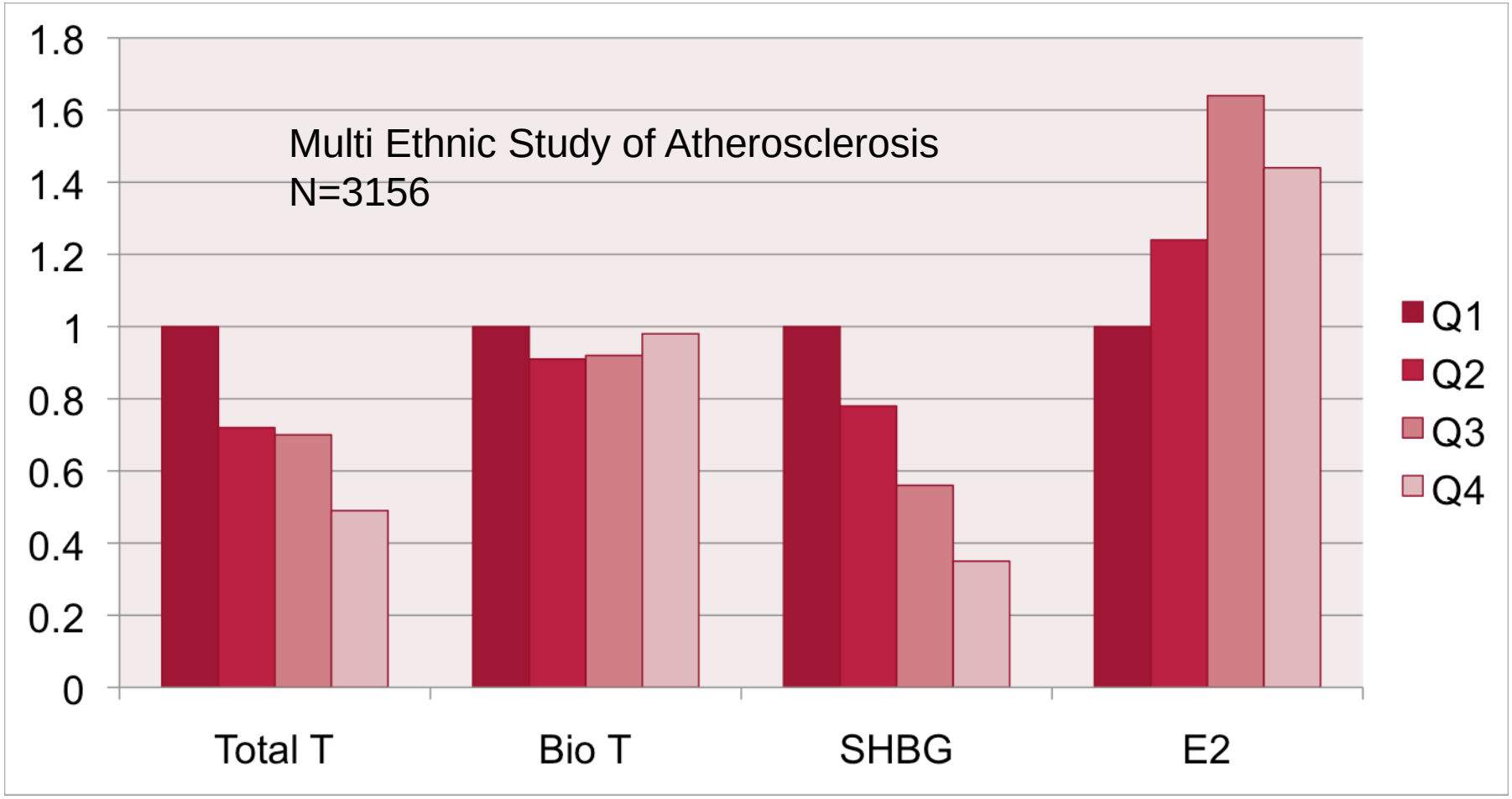
# Low TT Levels Predict Development of Metabolic Syndrome and Diabetes

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



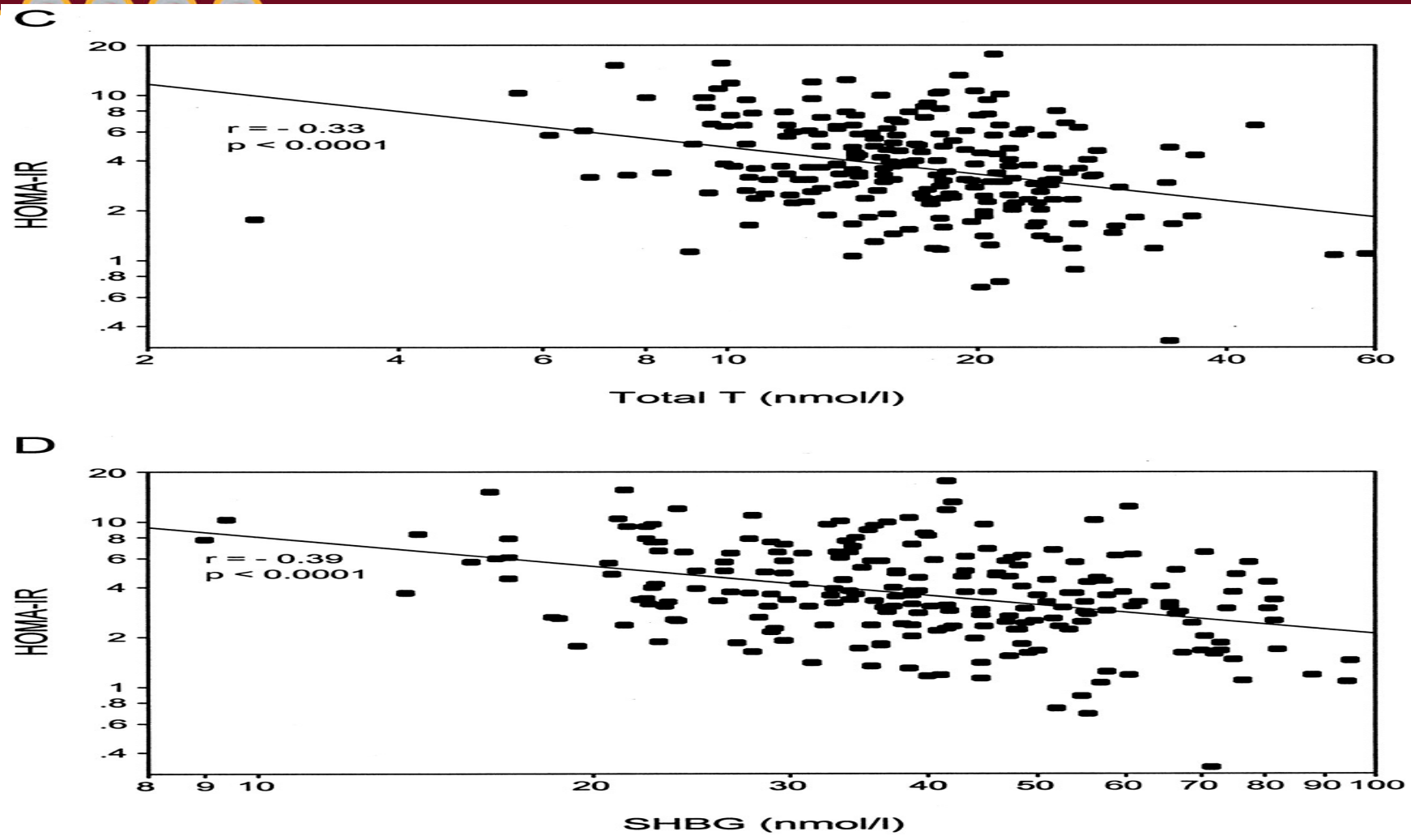

Laaksonen DE et al. *Diabetes Care.* 2004;27(5):1036-1041.

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



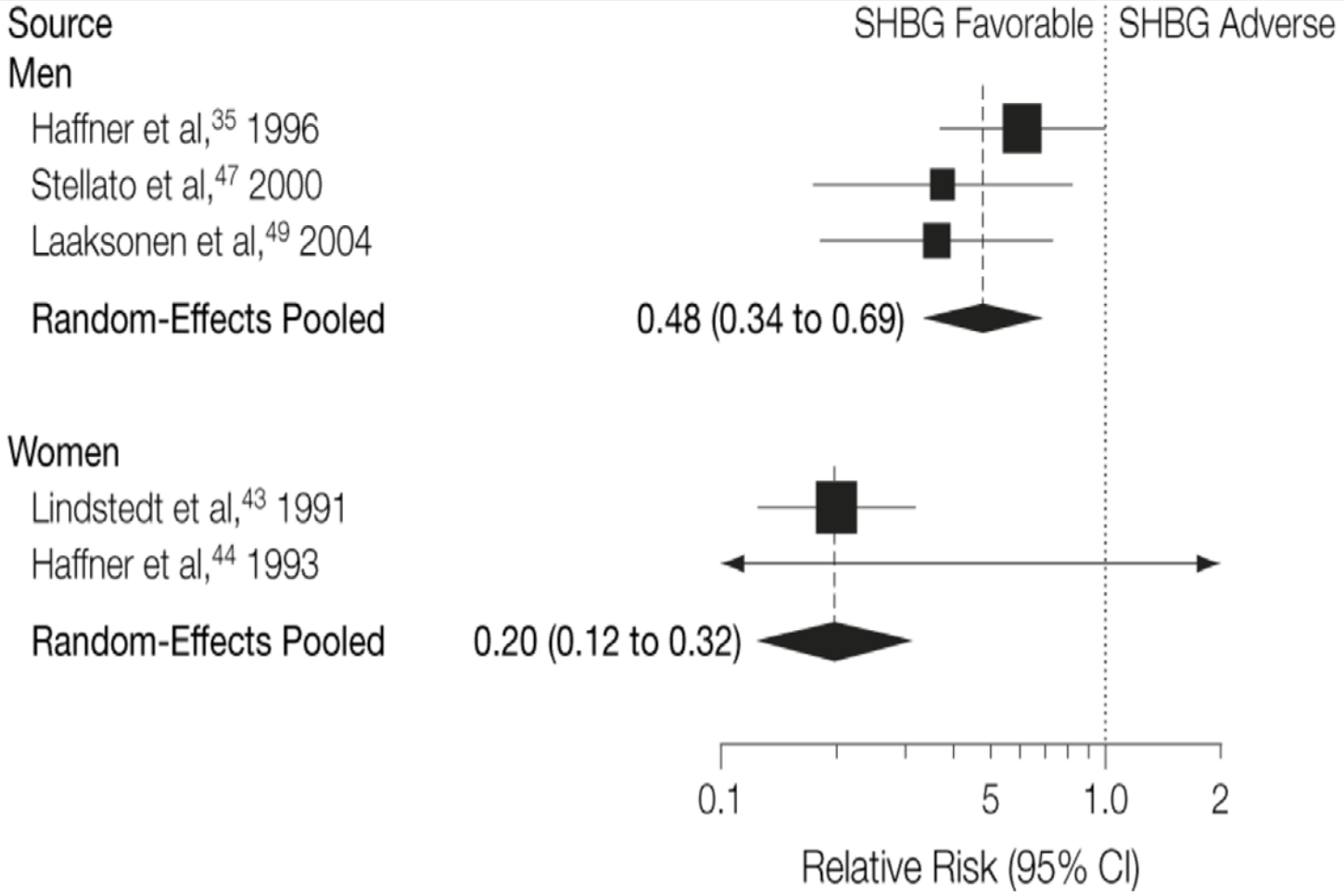

Colangelo, Diabetes Care 2009:32(6);1049-51

# Low Total T and SHBG are Correlated to Insulin Resistance (HOMA-IR)



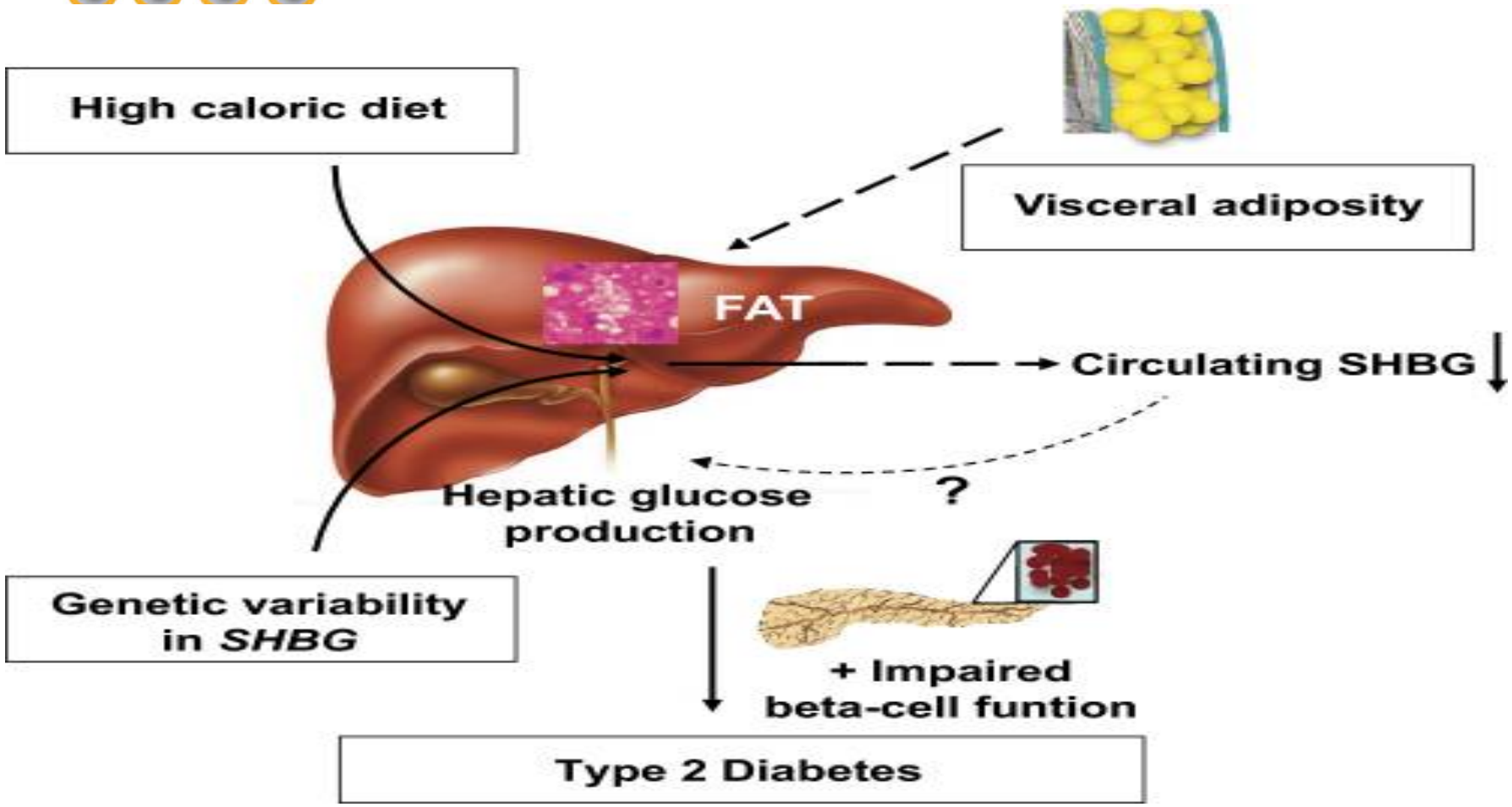

Tsai E C et al. Dia Care 2004;27:861-868

# Elevated SHBG Protects against Diabetes




Ding, JAMA 2006;295(11):1288-1299

# Low SHBG and Insulin Resistance: Cause or effect?




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**



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# 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 GLUT 1 receptor in vitro resulting in reduced insulin sensitivity
- Indirectly through changes in adipocity
  - 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



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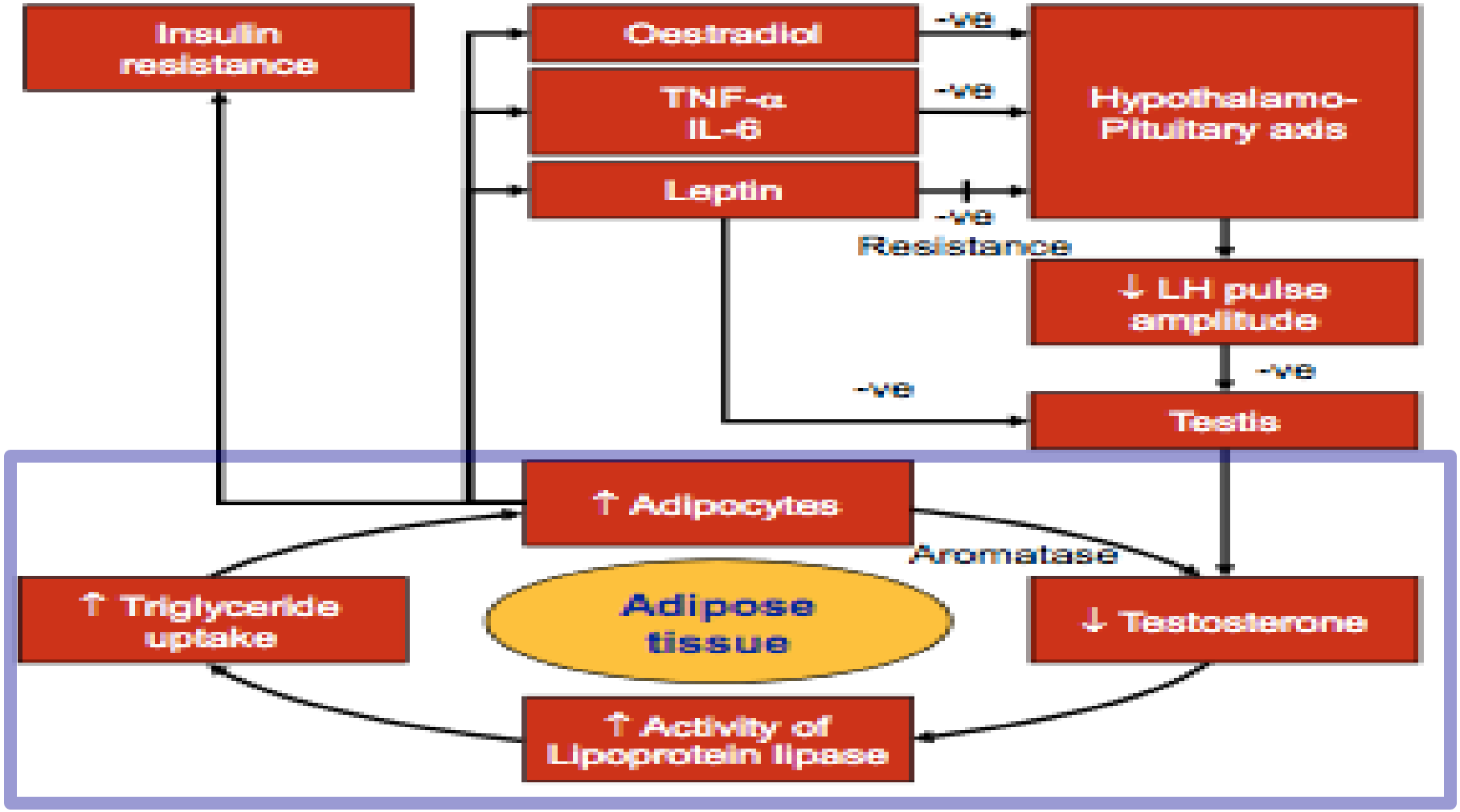
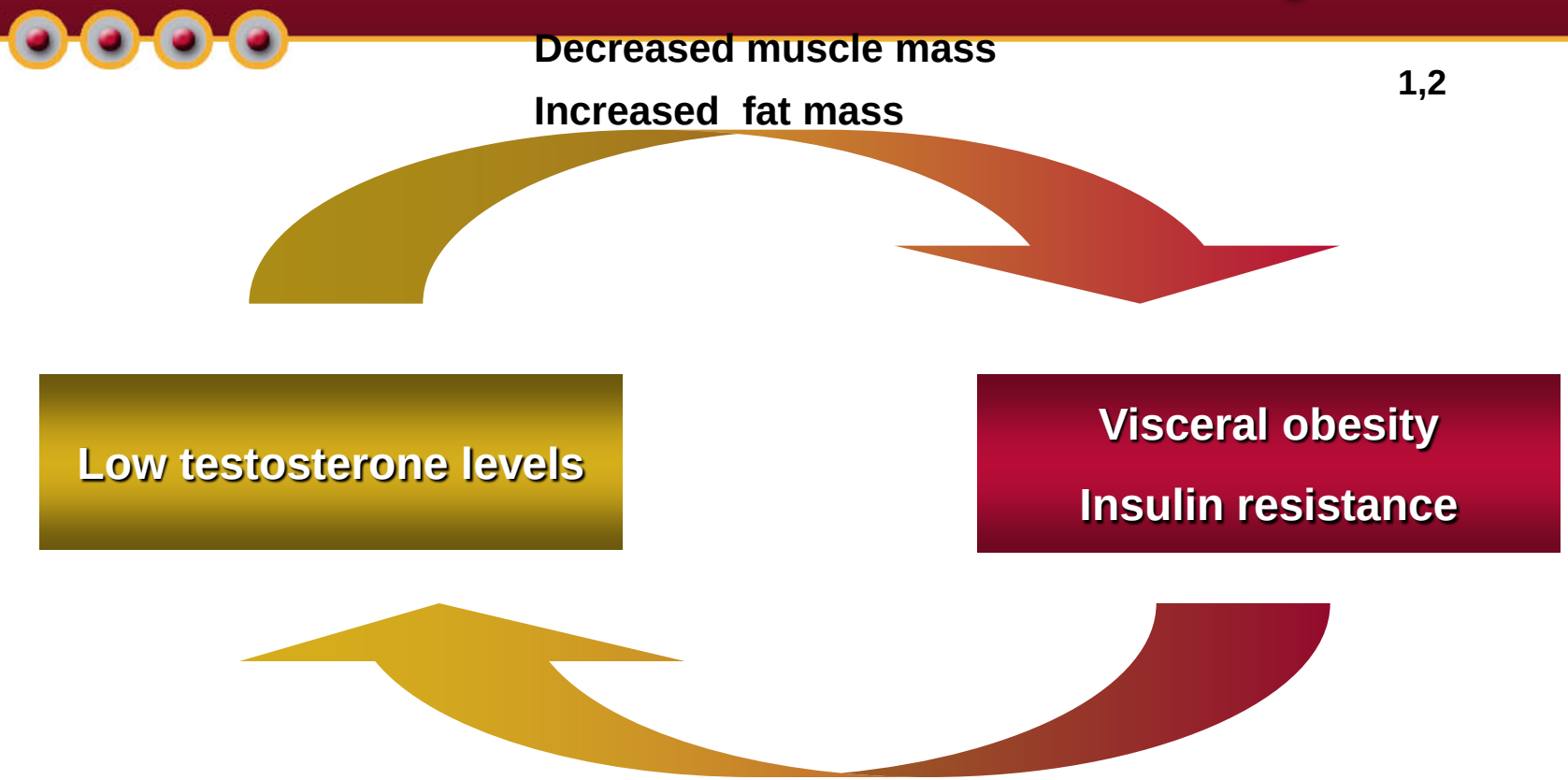
# Low T Causes Excess Adipocytes and Inflammation Causes Low T






Saad, Curr Diabetes Rev 2013;8:131- 143

# Vicious Circle: Bidirectionality of Low Testosterone and Obesity




1. Cohen PG. *Med Hypotheses.* 2001;56(6):702-708. 2. Wang C et al. *Diabetes Care.* 2011;34(7):1669-1675.

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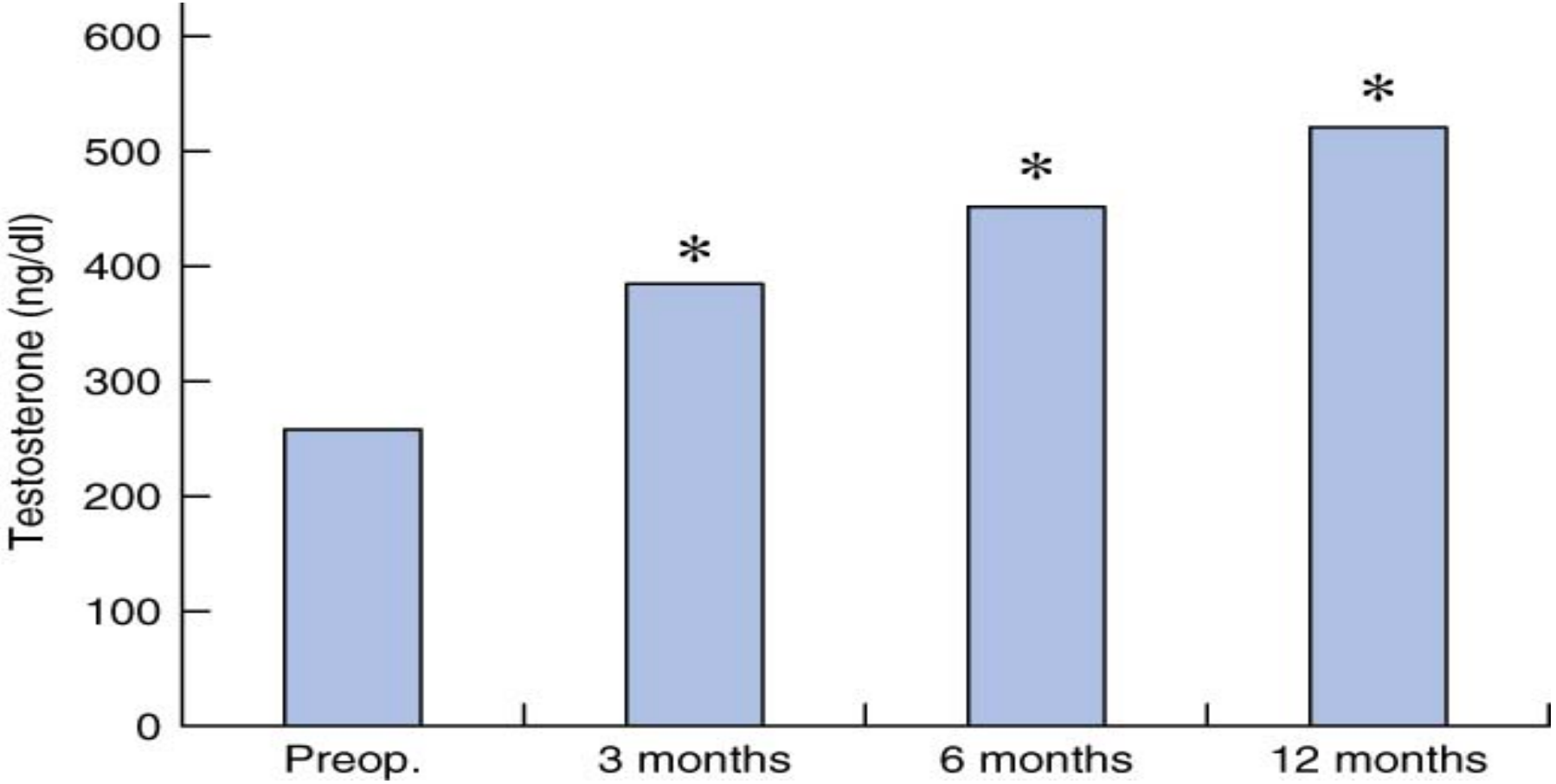
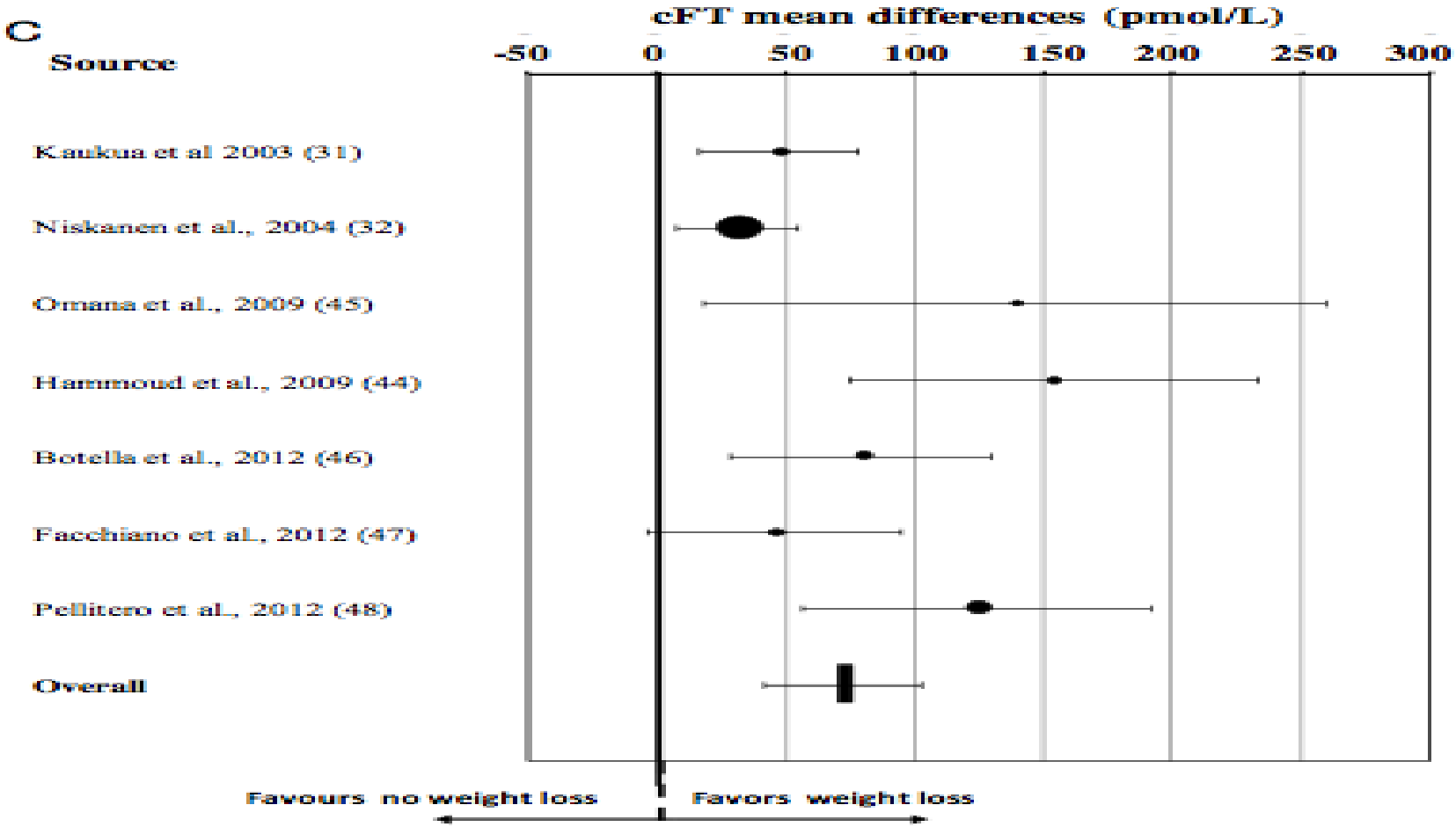
# Effect of Roux-en-Y gastric bypass on testosterone



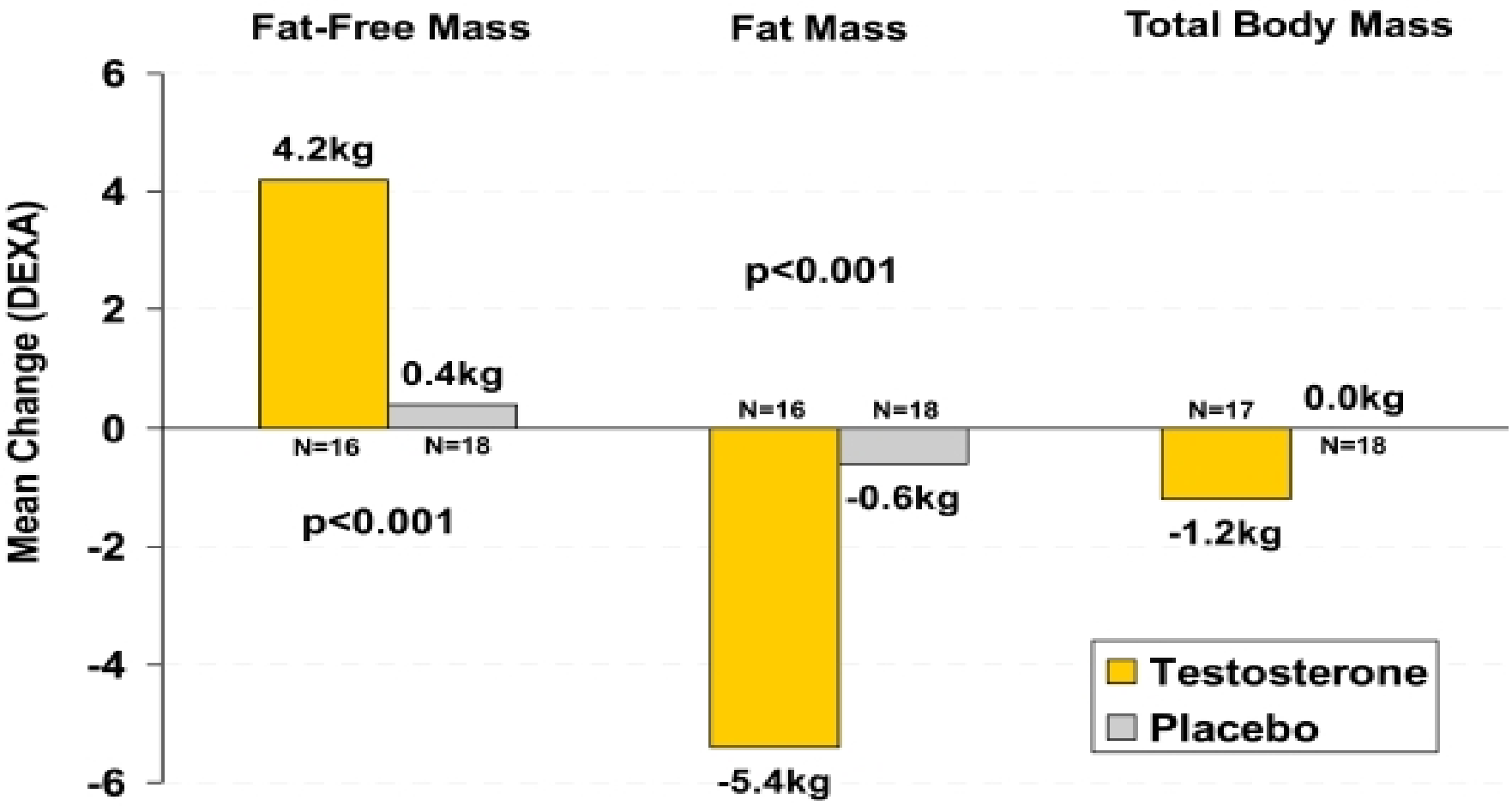

Woodard G, British Journal of Surgery 99:(5) 693-698, 2 FEB 2012

# Free Testosterone Increases with Weight Loss



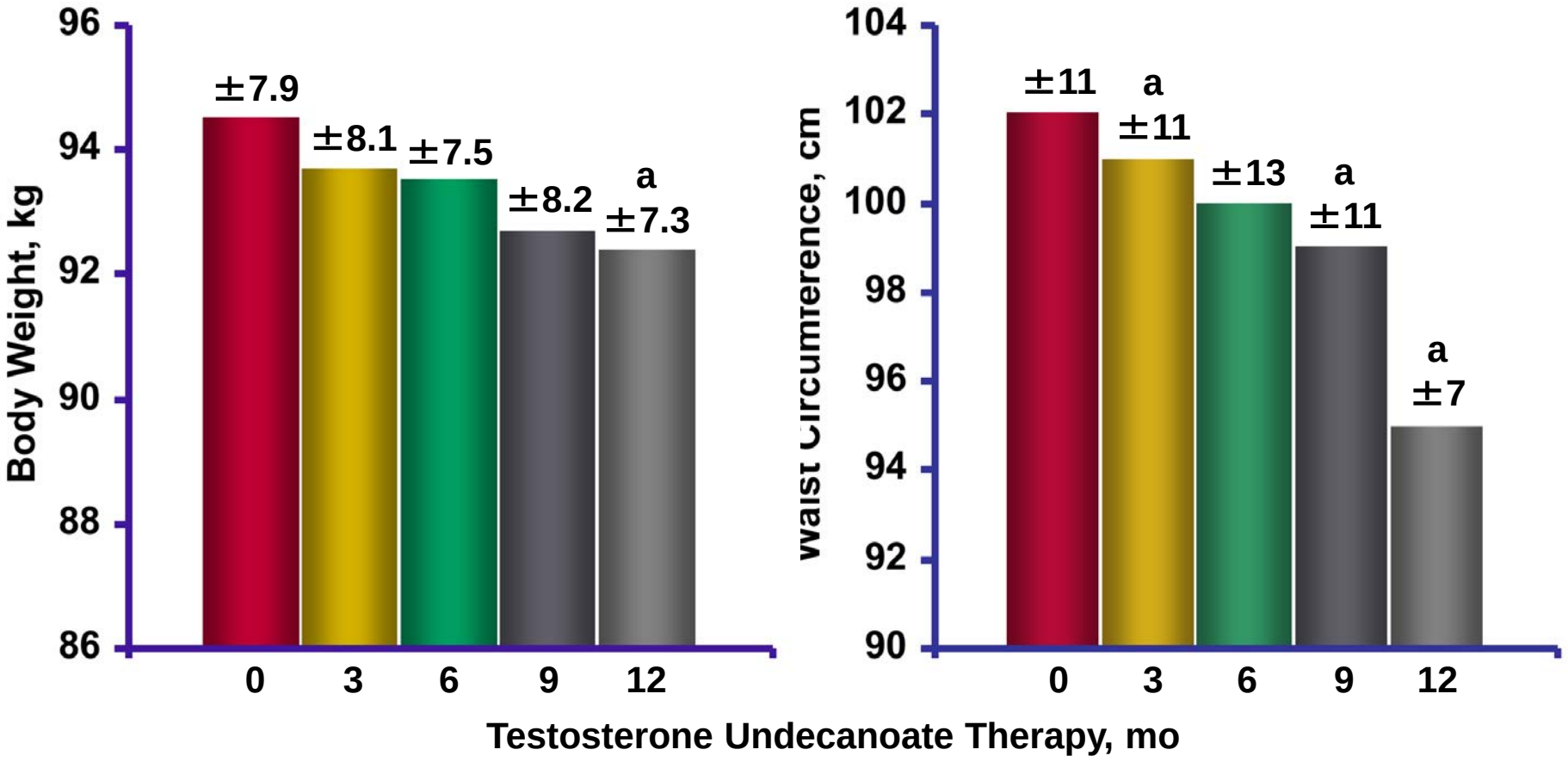

Corona, Eur J Endocrinol. 2013 Mar 12.

# Parenteral Testosterone Improves Body Composition in Elderly Men




Svartberg J, Int J Impot Res. 2008;20:378–87

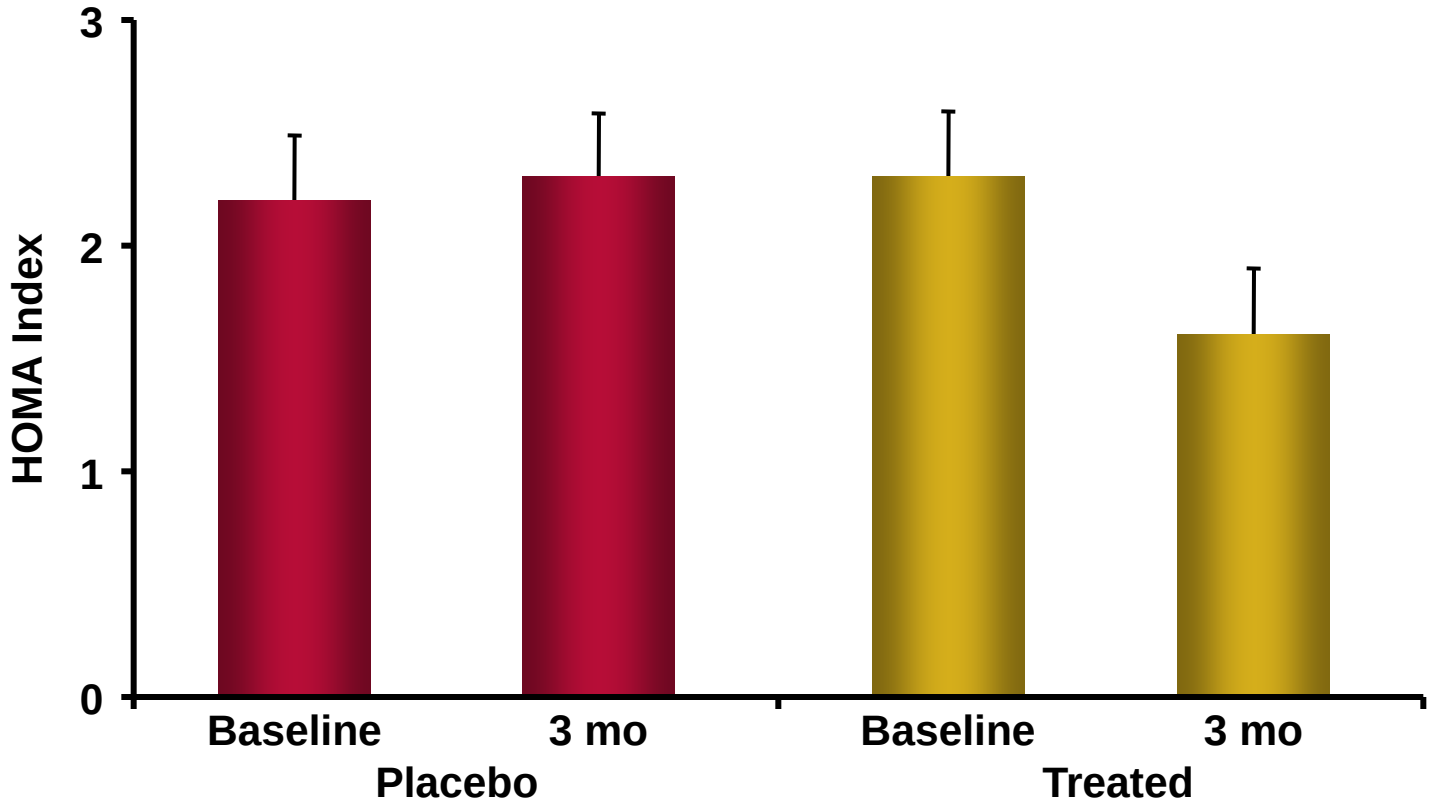
# Testosterone Therapy: Effect on Metabolic Syndrome Parameters




[a]*P*<.05 vs baseline.

Saad F et al. *Arch Androl*. 2007;53(6):353-357.

# Reduced Insulin Resistance after Testosterone Therapy in Diabetics

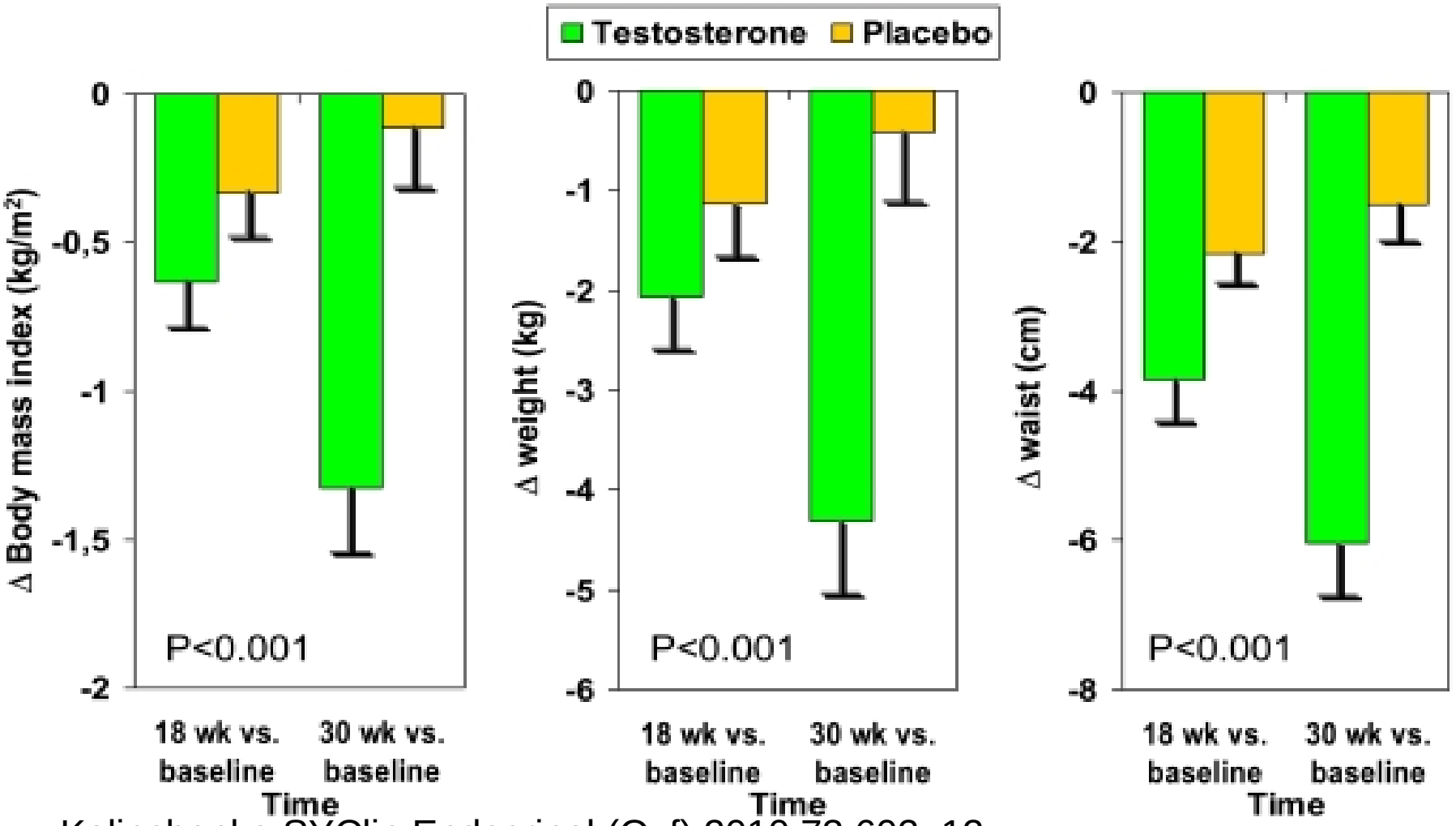



[a]HOMA-IR=fasting insulin × fasting glucose/22.5; HOMA was not measured in patients treated with insulin.

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

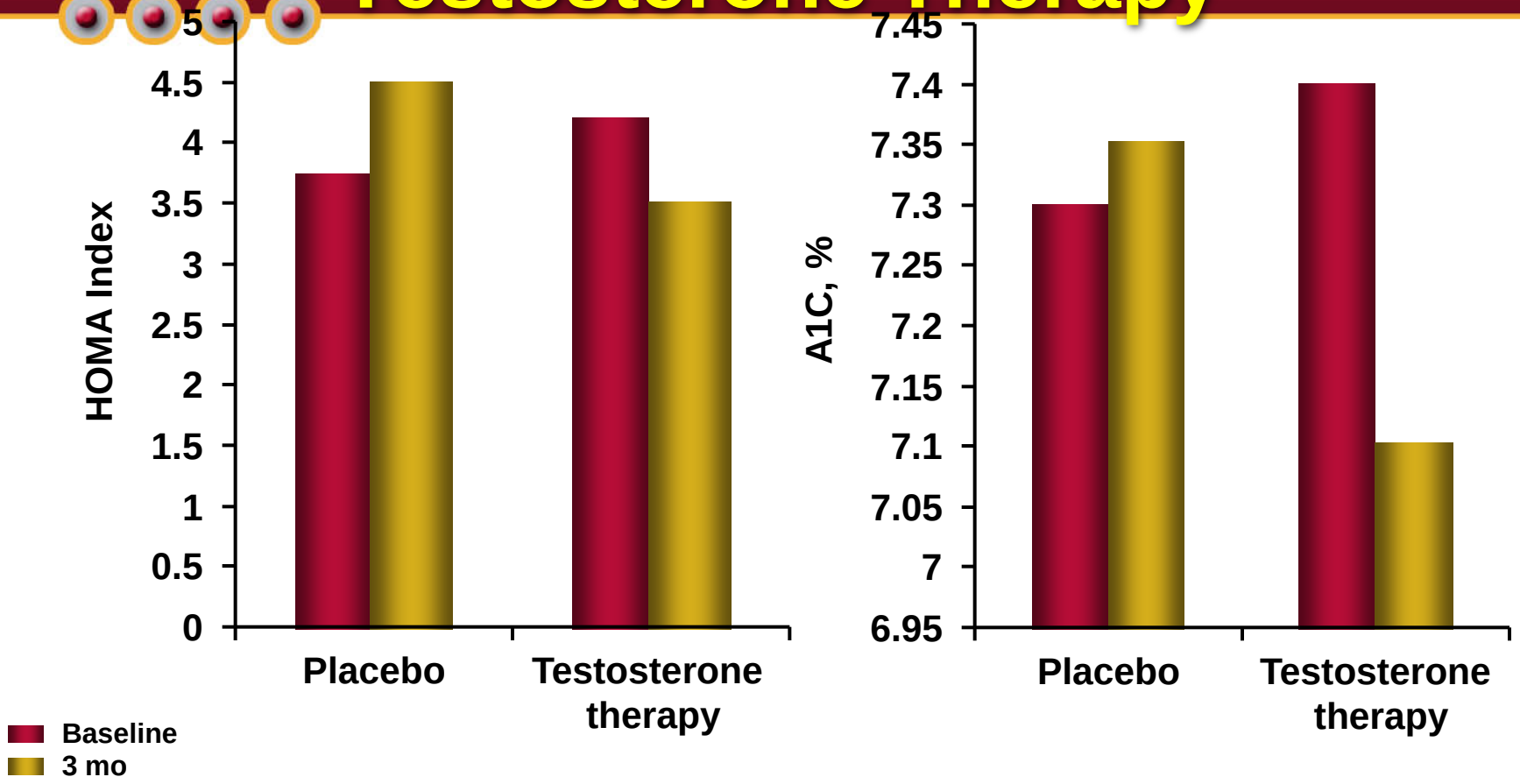
Reproduced from Cornoldi A et al. *Int J Cardiol.* 2010;142(1):50-55.

# Anthropometric Changes in a Double-Blind, Placebo-controlled Moscow Study in 184 Men with Metabolic Syndrome.




Kalinchenko SYClin Endocrinol (Oxf) 2010;73:602–12

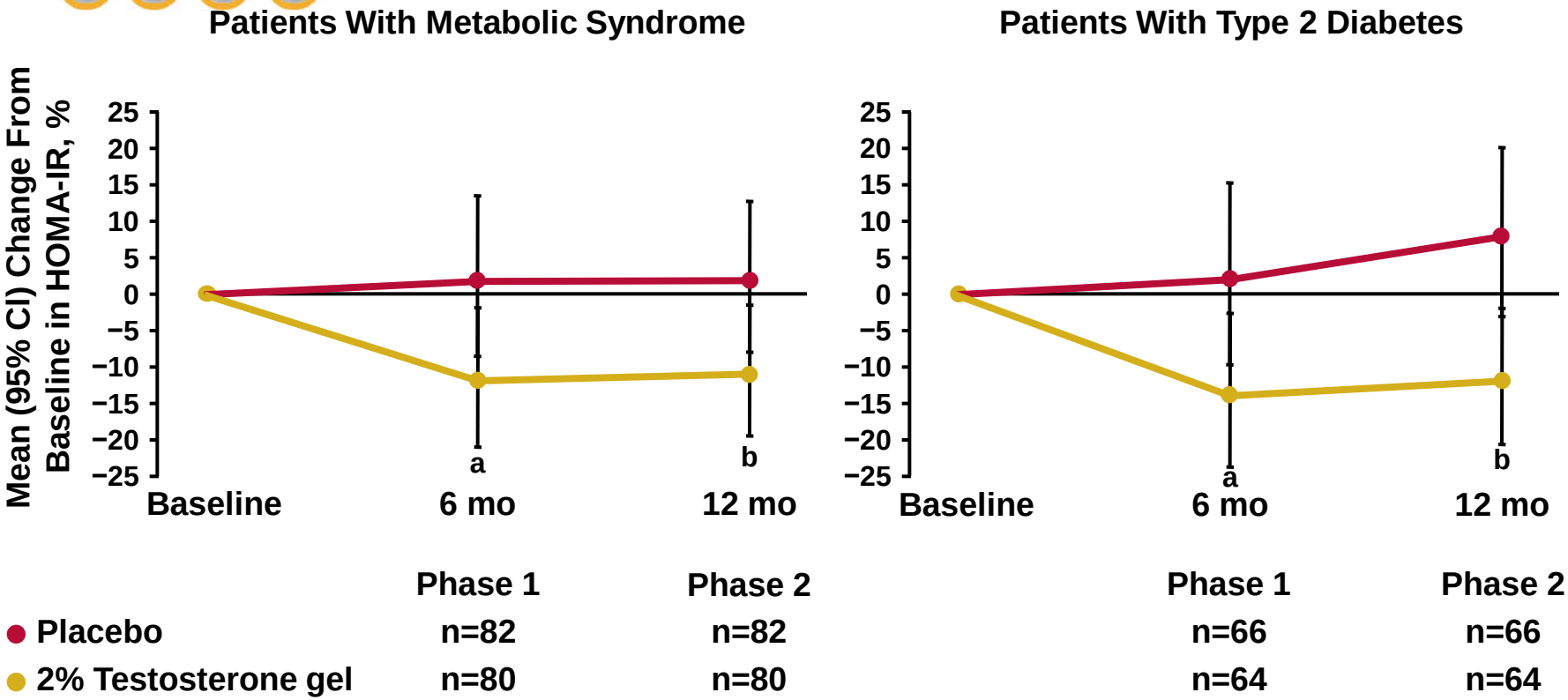
# Improved Glycemic Control in Hypogonadal Men Treated With Testosterone Therapy




A1C, glycosylated hemoglobin; HOMA, homeostasis model assessment.

Kapoor D et al. *Eur J Endocrinol*. 2006;154(6):899-906.

# Patients Treated With Testosterone Therapy




[a]*P*=.069.

[b]*P*=.054.

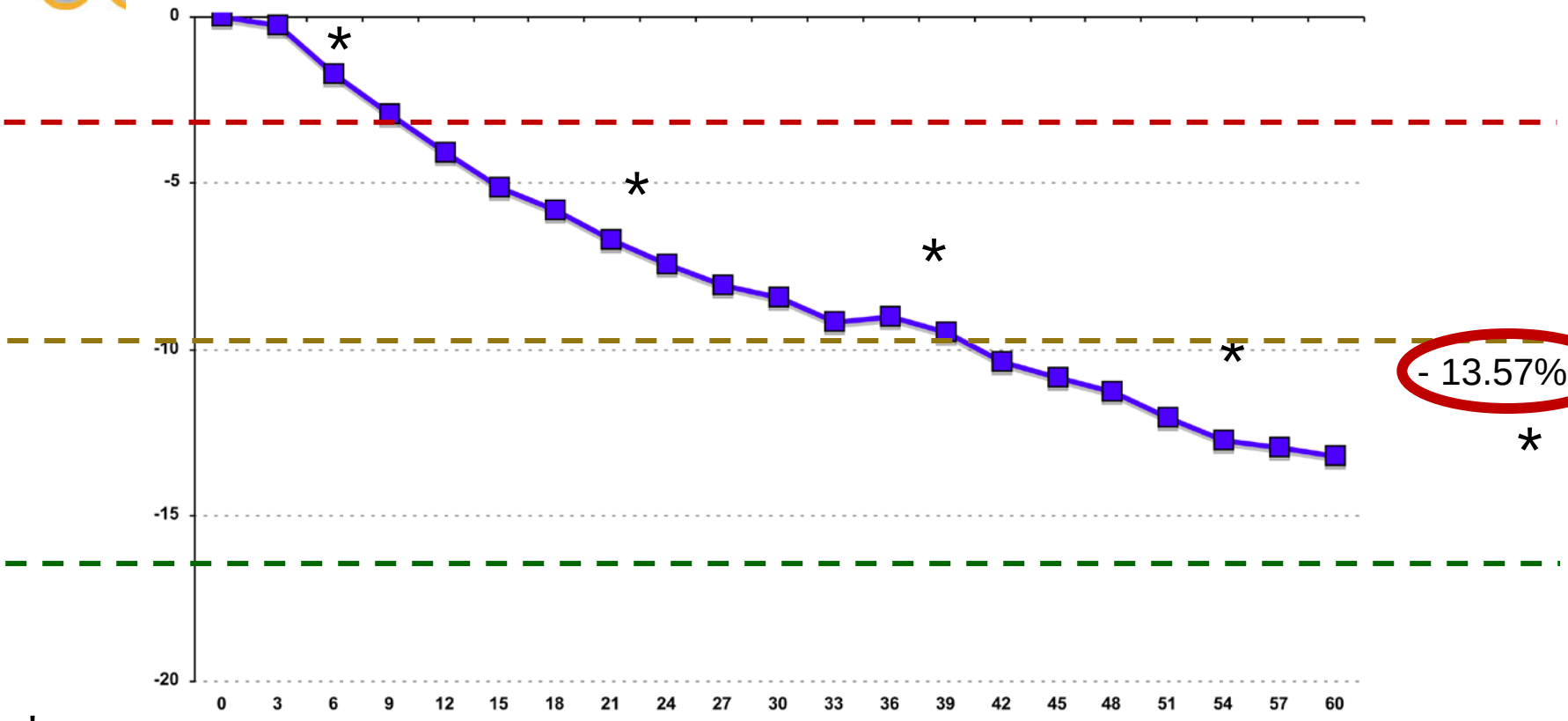
CI, confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance.

Jones TH et al. *Diabetes Care.* 2011;34(4):828-837.

# 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

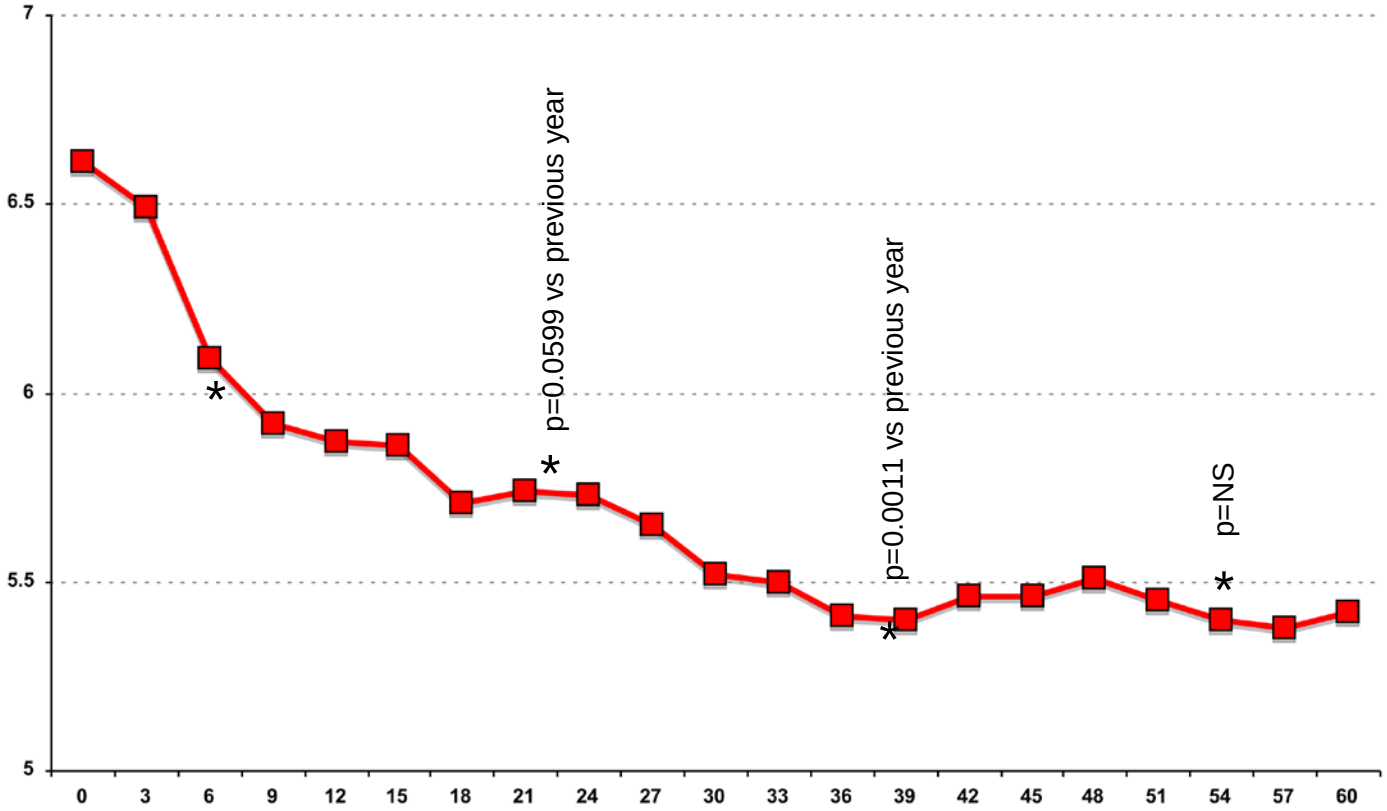



*p<0.0001 vs baseline

| N= | 255 | 255 | 251 | 228 | 215 | 200 | 182 | 172 | 148 | 135 | 116 |
|---|---|---|---|---|---|---|---|---|---|---|---|

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

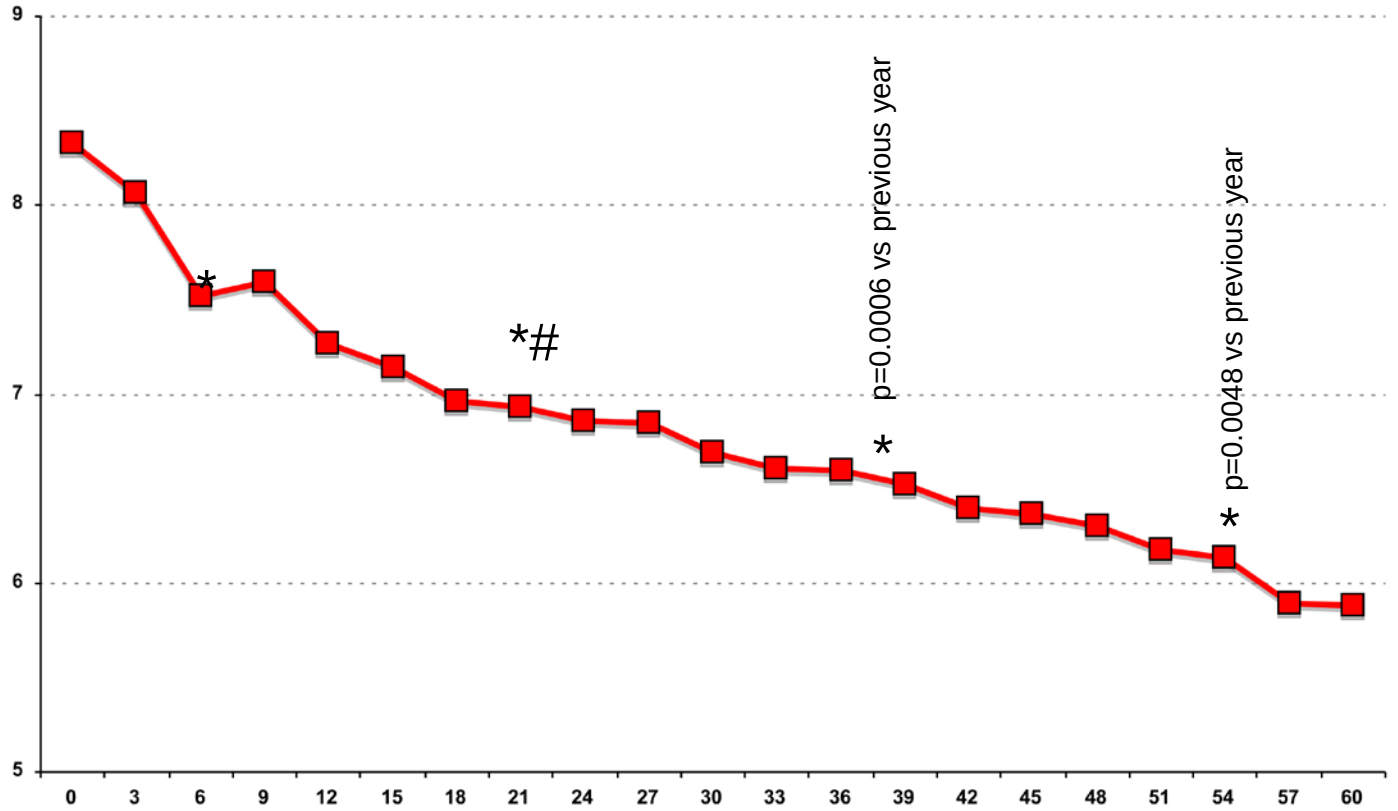



*p<0.0001 vs baseline # p<0.0001 vs previous year

| N= | 71 | 71 | 71 | 62 | 57 | 53 | 49 | 49 | 42 | 36 | 32 |
|---|---|---|---|---|---|---|---|---|---|---|---|

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

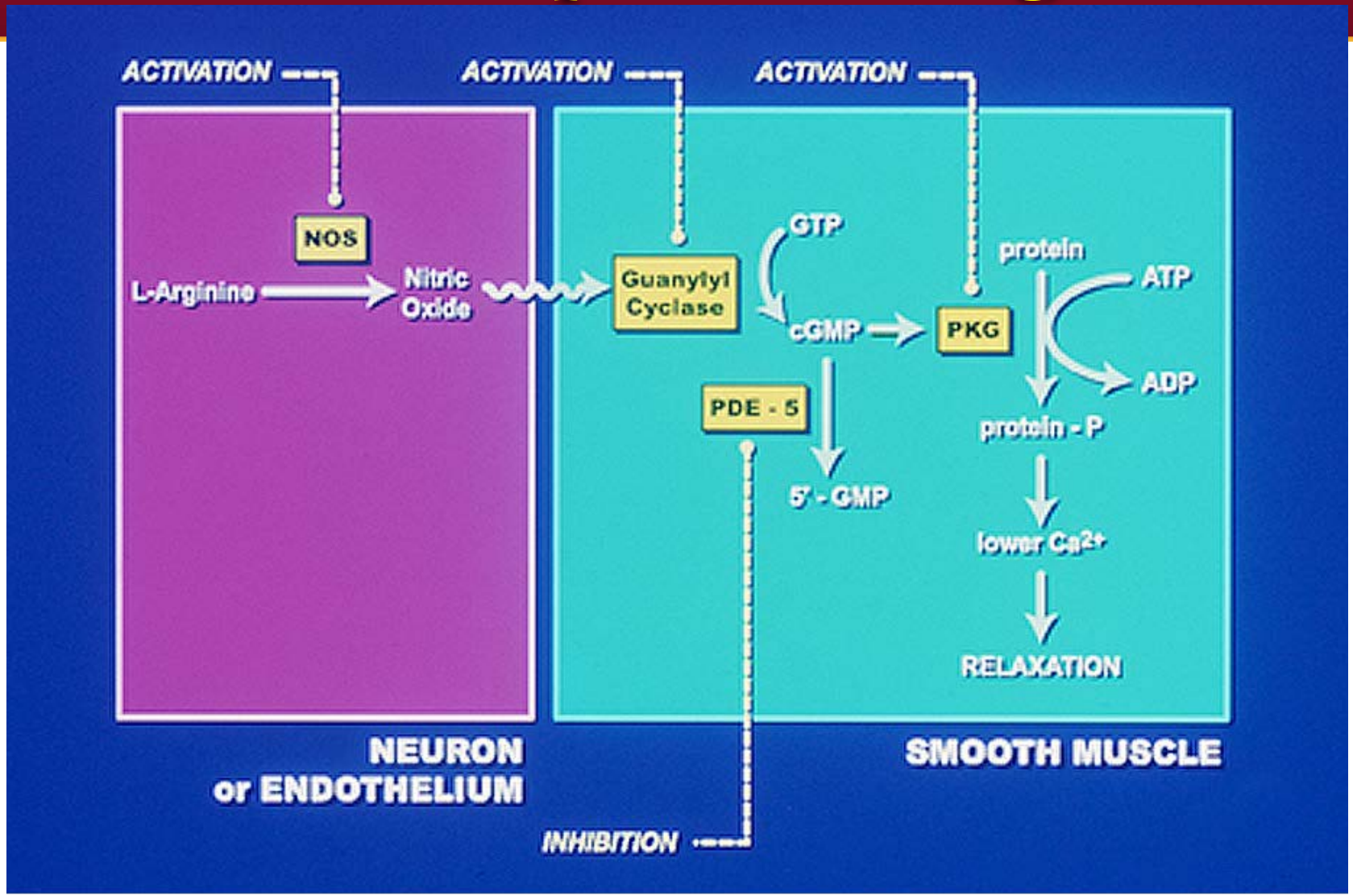



*p<0.0001 vs baseline # p<0.0001 vs previous year

| N= | 56 | 41 | 37 | 28 | 30 | 24 | 25 | 25 | 22 | 18 | 16 |
|---|---|---|---|---|---|---|---|---|---|---|---|

Saad F et al. Obesity, published online March 20, 2013

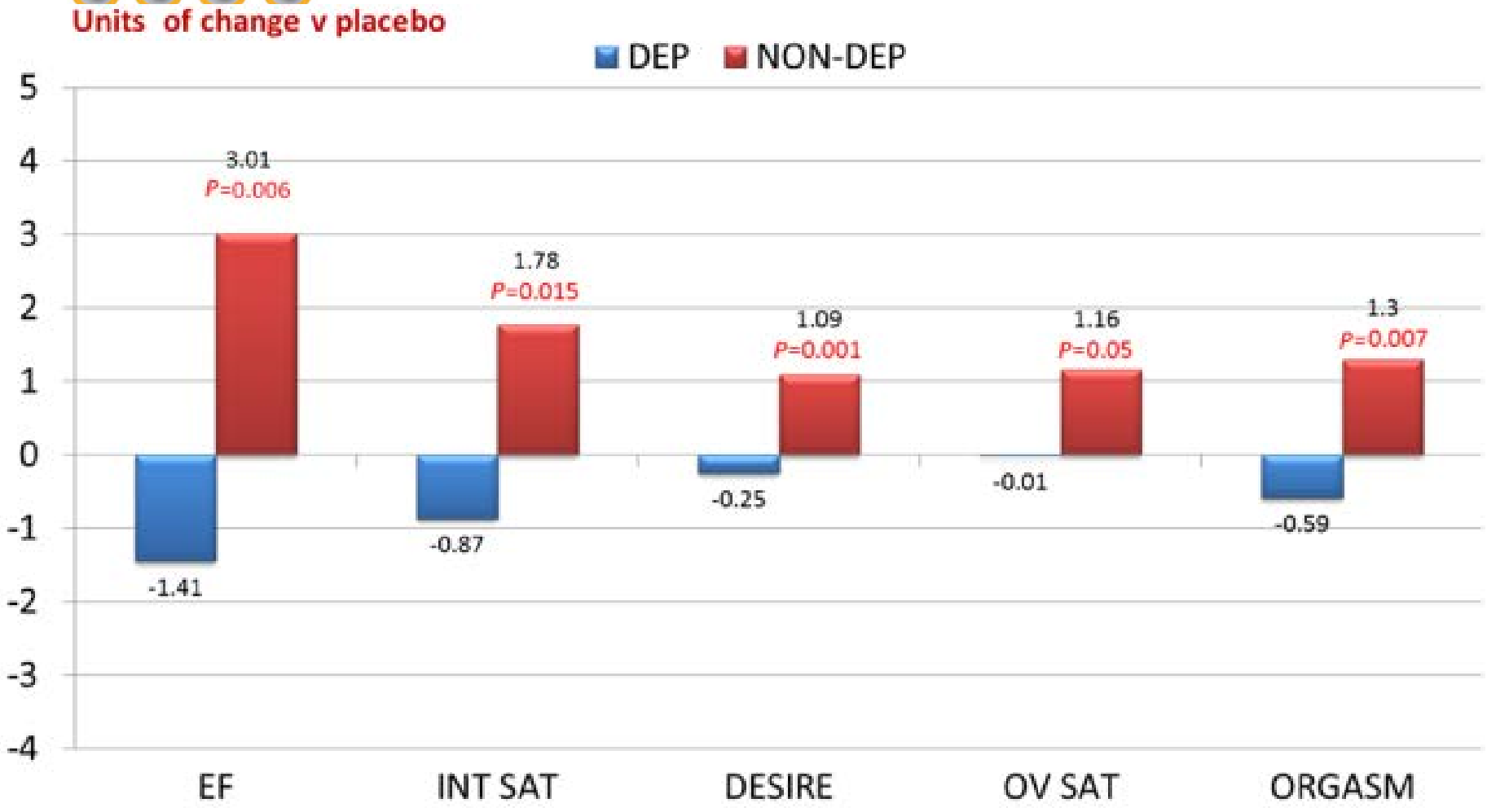
# Clinical Therapeutics: Target Sites



# 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 of Testosterone Replacement of Sexual Function in Men with DM

- **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.**

Hackett, J Sexual Med 2013; 10:6, 612–1627

# 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


1. Tsertsvadze A et al. Ann Intern Med 151:650-61, 2009
2. Morales A. J Urol 179:S103, 2008

# 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?**