WHEN TESTOSTERONE is the MISSING HORMONE in DIABETES MELLITUS

Hugh Jones

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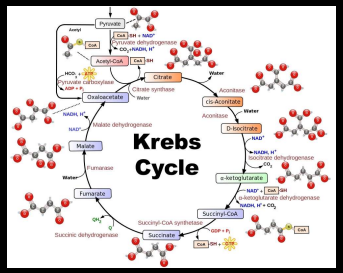
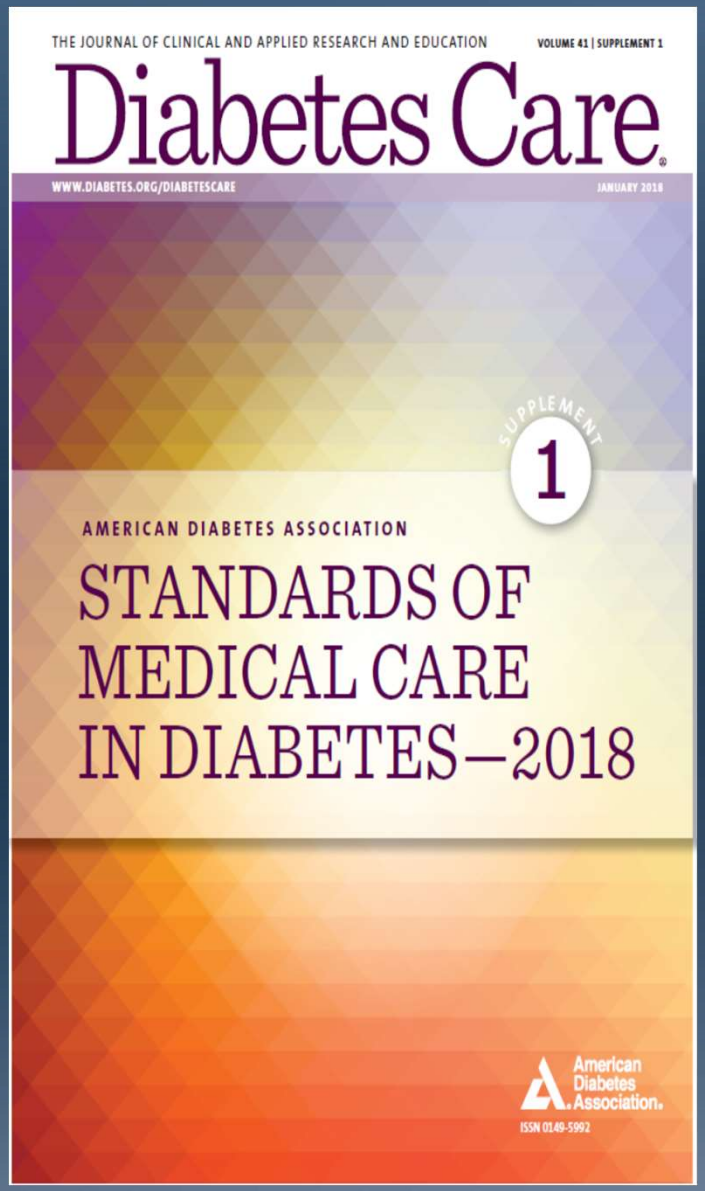
Academic Unit of Diabetes, Endocrinology & Metabolism, University of Sheffield

UNITED KINGDOM





Standards of Medical Care in Diabetes - 2018

American Diabetes Association®

Common Comorbidities

- Autoimmune Diseases (T1D)
- Cancer
- Cognitive Impairment/ Dementia
- Fatty Liver Disease
- Pancreatitis
- Fractures
- Hearing Impairment
- HIV
- Low Testosterone (Men)
- Obstructive Sleep Apnea
- Periodontal Disease
- Psychosocial/Emotional Disorders

Comprehensive Medical Evaluation and Assessment of Comorbidities:
Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S28-S37

Low Testosterone in Men: Recommendation

- In men with diabetes who have symptoms or signs of hypogonadism such as decreased sexual desire (libido) or activity, or erectile dysfunction, consider screening with a morning serum testosterone level. B

Comprehensive Medical Evaluation and Assessment of Comorbidities:
Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S28-S37

Testosterone Deficiency and Mortality in Men with Type 2 Diabetes

N=581

Total Testosterone

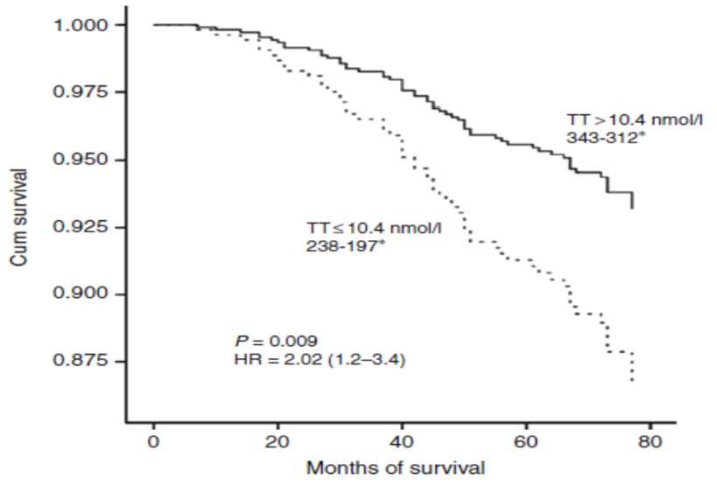


Figure 1 Multivariate-adjusted survival curves using Cox regression model for all-cause mortality based on total testosterone (TT). The solid line represents male subjects with a baseline TT >10.4 nmol/l and the broken line represents TT ≤10.4 nmol/l. HR, hazard ratio for decreased survival after adjusting for BMI, HbA1c, pre-existing cardiovascular disease, smoking, statin and ACEI/ARB therapy. *The number of patients alive at the start of the study and at the end of the study.

Bioavailable Testosterone

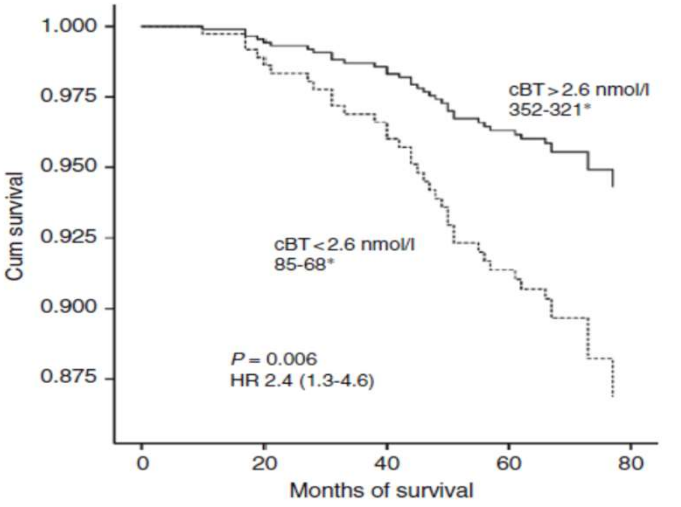


Figure 2 Multivariate-adjusted survival curves using Cox regression model for all-cause mortality based on calculated bioavailable testosterone (cBT). The solid line represents male subjects with a baseline cBT >2.6 nmol/l and the broken line represents cBT ≤2.6 nmol/l. HR, hazard ratio for decreased survival after adjusting for BMI, HbA1c, pre-existing cardiovascular disease, smoking, statin and ACEI/ARB therapy. *The number of patients alive at the start of the study and at the end of the study of a total of 437 patients analysed.

Multivariate-adjusted survival curves

BMI

HbA1c

Smoking

Statin Therapy

ACEI/ARB Rx

Pre-existing CVD

Cardiovascular Mortality Sub-Analysis

TT<8.4nmol/l HR 2.5 (p=0.02)

Muraleedharan V, Marsh HA, Kapoor D, Channer KS, Jones TH Eur J Endocrinol 2013 166;725-733

In Older Men an Optimal Plasma Testosterone Is Associated With Reduced All-Cause Mortality and Higher Dihydrotestosterone With Reduced Ischemic Heart Disease Mortality, While Estradiol Levels Do Not Predict Mortality

Bu B. Yeap, Helman Alfonso, S. A. Paul Chubb, David J. Handelsman, Graeme J. Hankey, Osvaldo P. Almeida, Jonathan Golledge, Paul E. Norman, and Leon Flicker

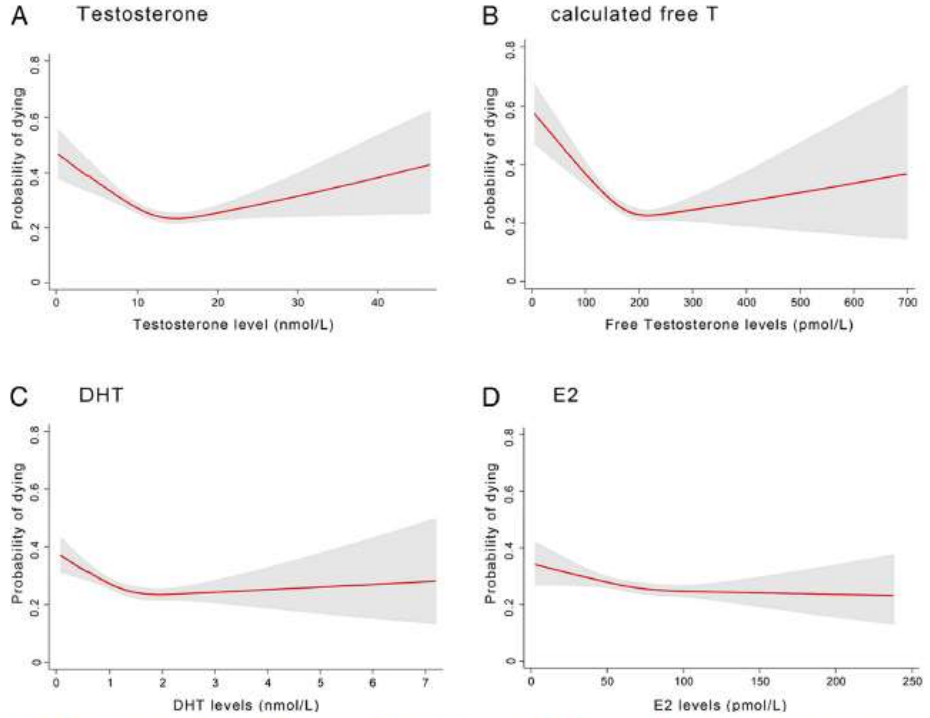


Figure 2. Probability of dying from any cause according to plasma levels of T (A), calculated free T (B), DHT (C) and estradiol (D) in 3690 community-dwelling men aged 70 to 89 years.

WADLS captures mortality data for the entire state of ments as the use of medication for hypertension, hyper-

N=3690

Death 974

Of which 325 were CHD deaths

JCEM 99;E9-E18 2014

EDITOR'S CHOICE

PRESS RELEASE

Low serum testosterone and increased mortality in men with coronary heart disease

Chris J Malkin,[1] Peter J Pugh,[1] Paul D Morris,[1] Sonia Asif,[1] T Hugh Jones,[2,3] Kevin S Channer[1]

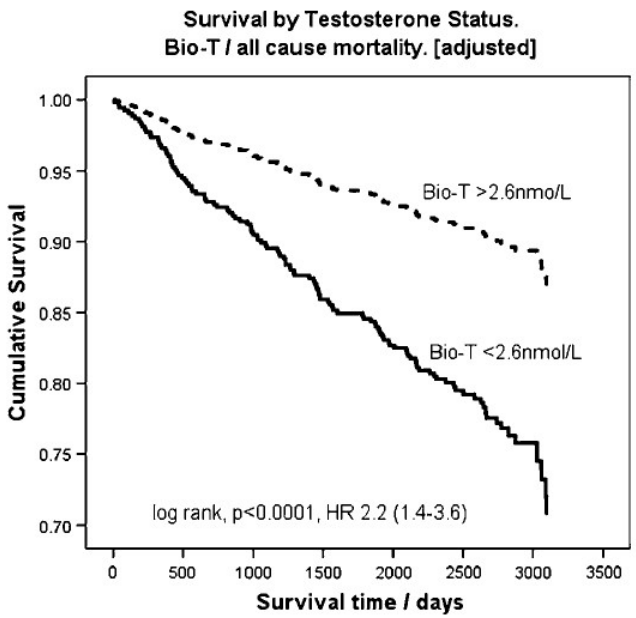


Figure 1 Shows a survival curve of all-cause mortality based on baseline bio-available testosterone (bio-T). The solid line represents patients with baseline bio-T less than 2.6 nmol/l, the broken line represents patients with bio-T greater than 2.6 nmol/l. HR, hazard ratio.

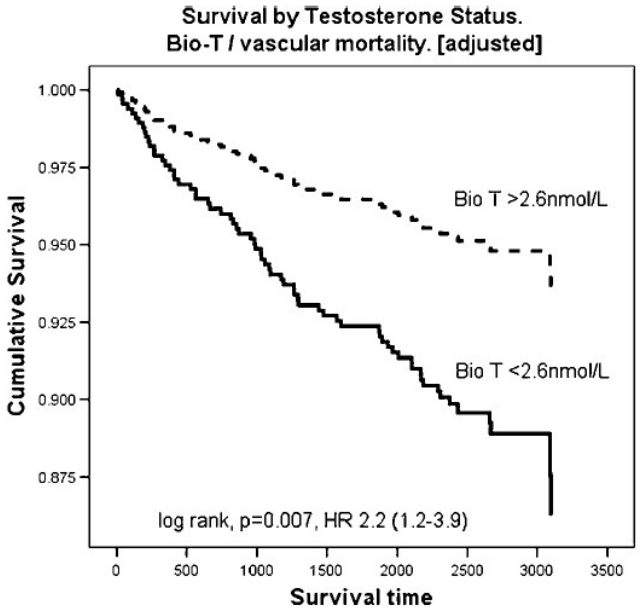
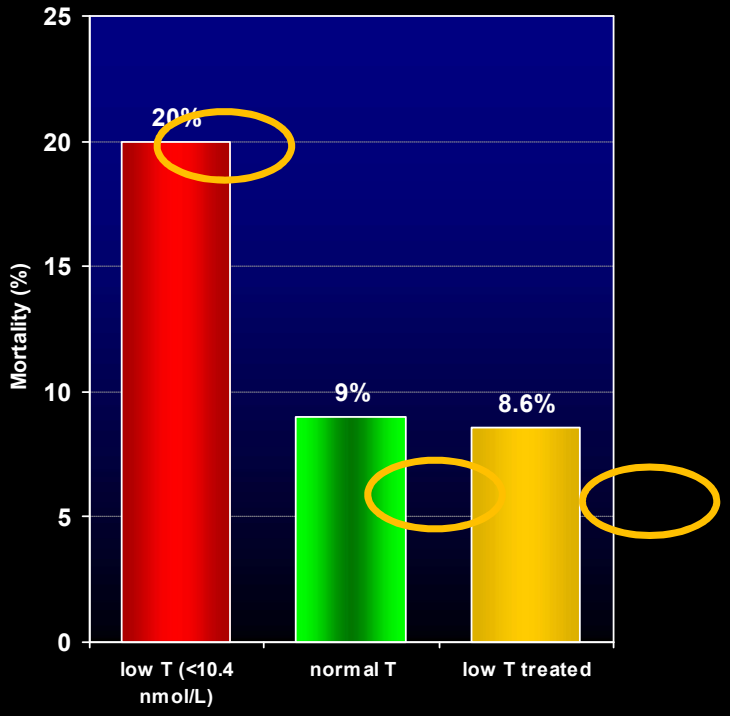


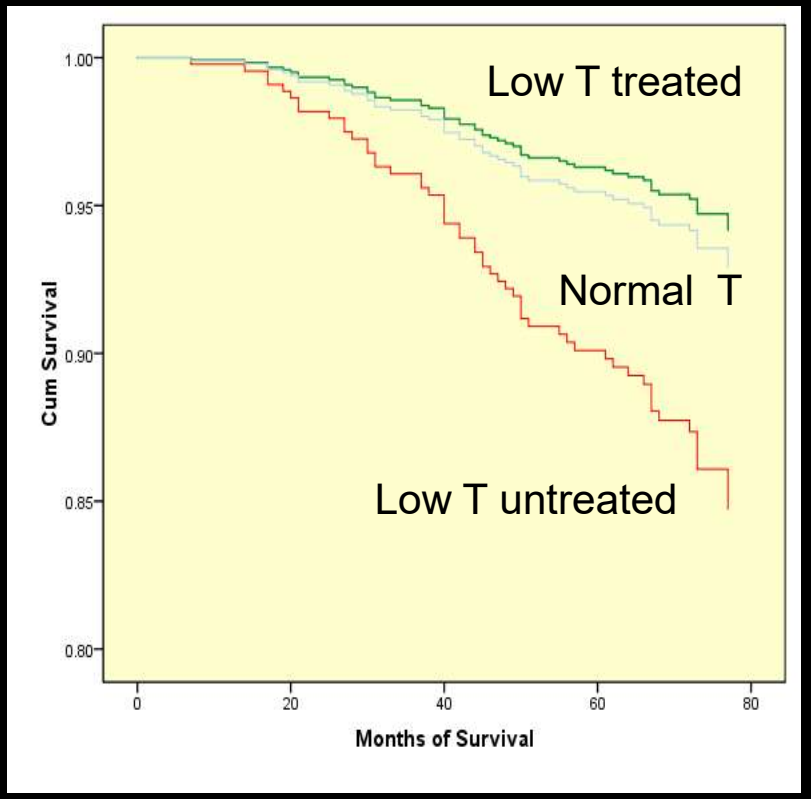
Figure 2 Shows a survival curve of vascular mortality based on baseline bio-available testosterone (bio-T). The solid line represents patients with baseline bio-T less than 2.6 nmol/l, the broken line represents patients with bio-T greater than 2.6 nmol/l. HR, hazard ratio.

N=930

Malkin CJ et al. Heart 2010;96:1821-25

Low Testosterone Predicts Increased Mortality and Testosterone Therapy Improves Survival in Men with Type 2 Diabetes (mean Follow-up: 5.8 years, n=587)





Cardiovascular Mortality Sub-Analysis
TT<8.4nmol/l HR 2.5 (p=0.02)

Multivariate-adjusted survival curves

BMI
HbA1c
Smoking
Statin Therapy
ACEI/ARB Rx
Pre-existing CVD

Muraleedharan V et al. Eur J Endocrinol 2013;169:6

Hypogonadism is a clinical syndrome which comprises both symptoms ± signs and biochemical evidence of testosterone deficiency.

Table 3.3 Endocrine Society's Clinical Guidelines classification of symptoms and signs of androgen deficiency

A. Symptoms and signs suggestive of androgen deficiency	B. Symptoms and signs associated with androgen deficiency that are less specific
↓ Sexual desire (libido) and activity	↓ Energy, motivation, initiative, aggressiveness, self-confidence
↓ Spontaneous erections	Feeling sad or blue, depressed mood, dysthymia
Breast discomfort, gynaecomastia	Poor concentration and memory
Loss of axillary and pubic hair, ↓ shaving	Sleep disturbance, ↑ sleepiness
Very small or shrinking testes (especially <5 ml)	Mild anaemia (normochromic, normocytic)
Incomplete sexual development, eunuchoidism aspermia	↑ body fat, ↑ body mass index
Inability to father children, low or zero sperm counts	Diminished physical or work performance
Height loss, low trauma fracture, ↓ bone mineral density	
↓ muscle bulk and strength	
Hot flushes, sweats	

Clinical Manifestations of Hypogonadism

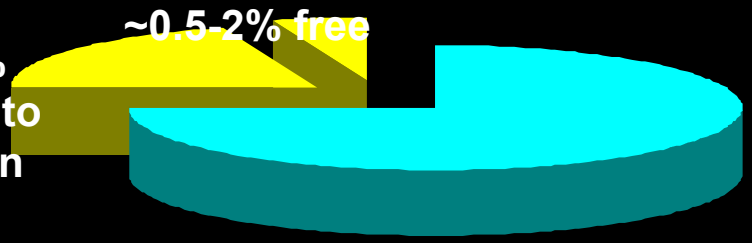
Physical	Psychological	Sexual
• Decreased bone mineral density • Decreased muscle mass and strength • Gynaecomastia • Anaemia • Frailty • Increased body fat, body mass index • Fatigue	• Depressed mood • Diminished energy, sense of vitality or well-being • Impaired cognition and memory	• Diminished libido • Erectile dysfunction • Difficulty achieving orgasm • Decreased performance

AACE Hypogonadism Task Force. *Endocr Pract*. 2002;8:439-456. Bhasin S et al. *J Clin Endocrinol Metab*. 2006;91:1995-2010

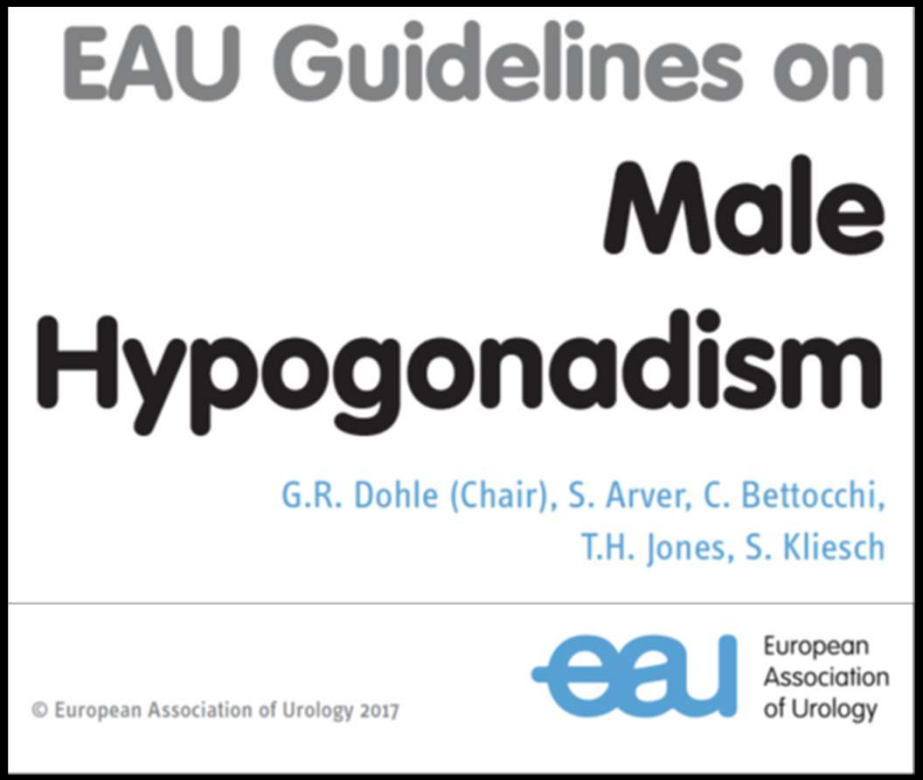
Serum Testosterone

Bioavailable Testosterone

Biologically Inactive?



60-80% bound to SHBG



A LIVING GUIDELINE

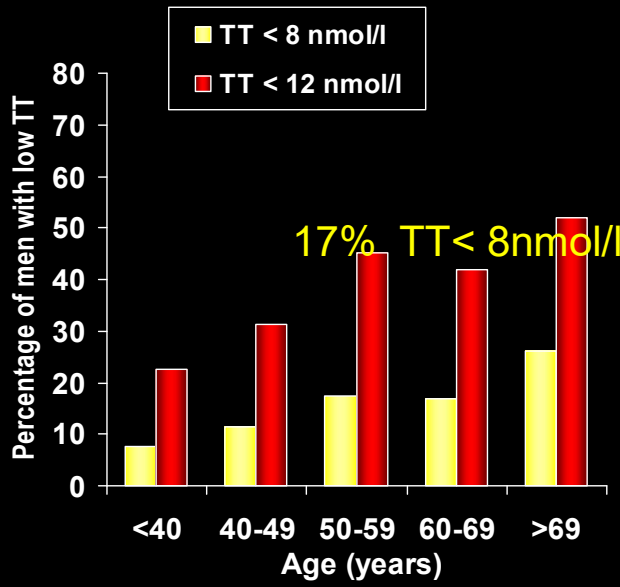
Fully revised every TWO years with any important updates yearly

www.uroweb.org/guidelines/male-hypogonadism/

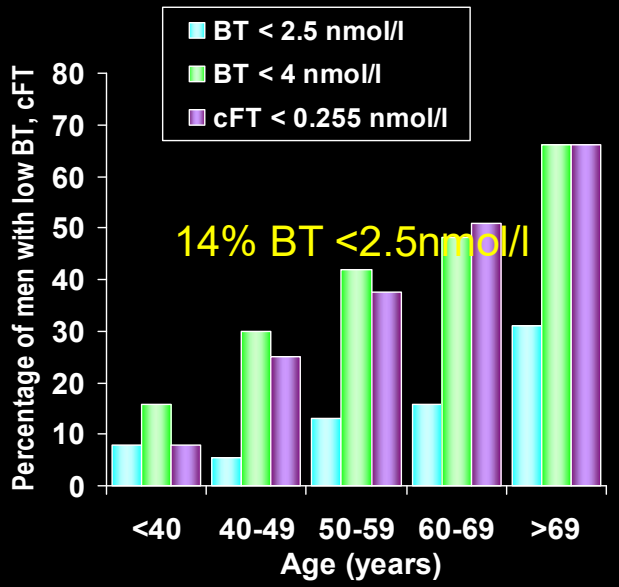
Recommendations—diagnosis	LoE	Grade
Restrict diagnosis of TD to men with persistent symptoms suggesting TD and confirmed low T	3	C
Measure fasting T levels in the morning before 11 AM, acknowledging that, in normal life, non-fasting levels could be up to 30% lower	2	A
Repeat TT assessment on ≥2 occasions by a reliable method; in addition, measure FT in men with levels close to the lower normal range (8–12 nmol/L) or those with suspected or known abnormal SHBG levels	1	A
Measure LH serum levels to differentiate primary from secondary TD	2	A
Base decisions on therapy on published action levels rather than laboratory reference ranges	4	B

Prevalence of Symptomatic Hypogonadism in Men with Type 2 Diabetes

Total testosterone (TT)



Bioavailable testosterone (BT) and calculated free testosterone (cFT)



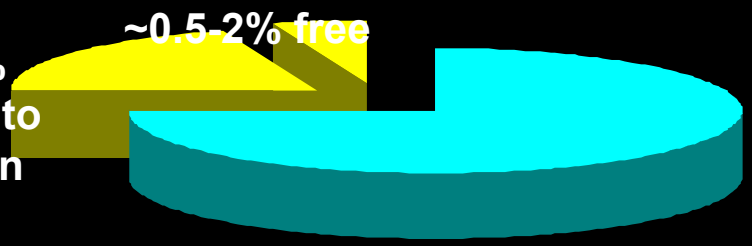
Total T nmol/l 12.72 + 0.29 (2.9 – 39) NR 8.3-41
SHBG nmol/l 32.48 + 1.06 (5.14-129) NR 15-100

Kapoor D et al. Diabetes Care 30: 911–917 (2007)

Serum Testosterone

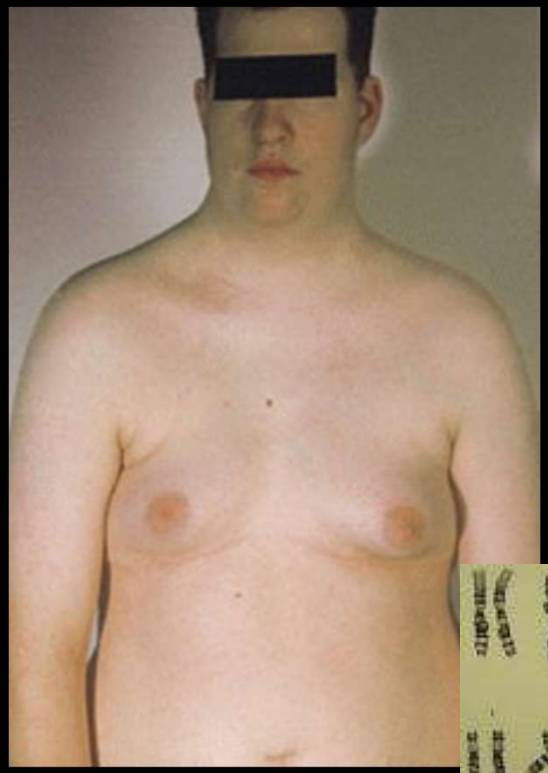
Bioavailable Testosterone

Biologically Inactive?

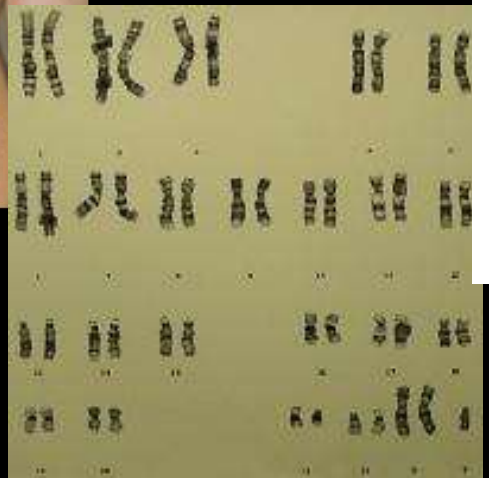


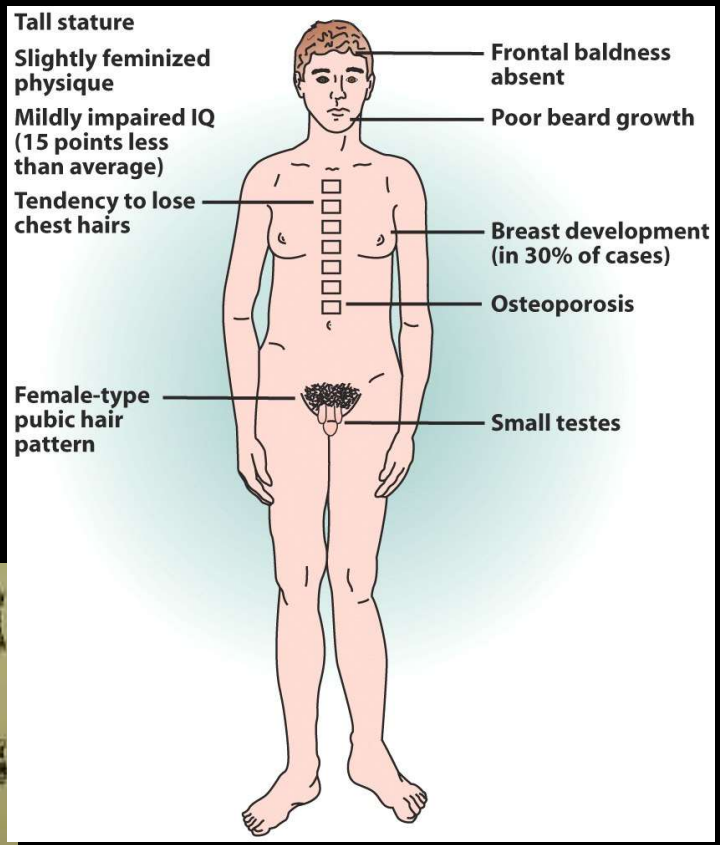
60-80% bound to SHBG

Klinefelter's Syndrome



1 in 500 male births

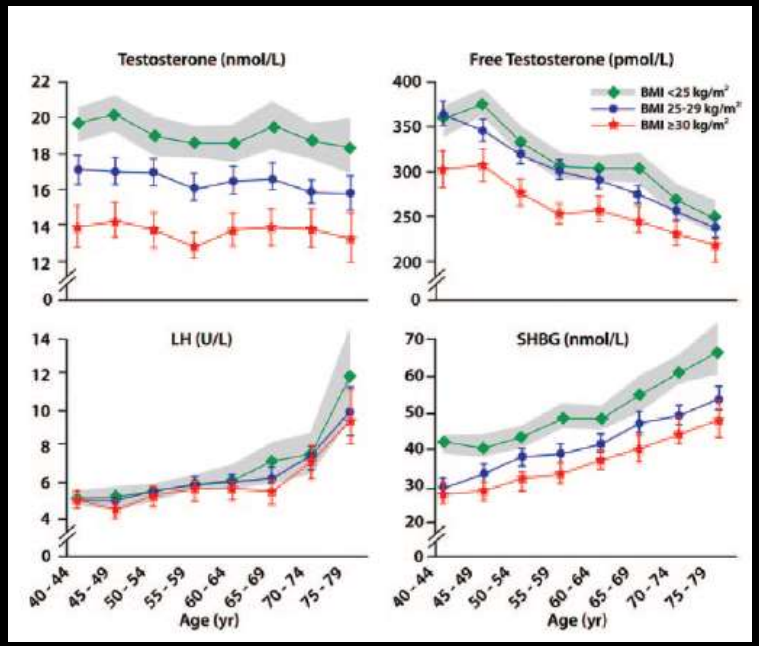




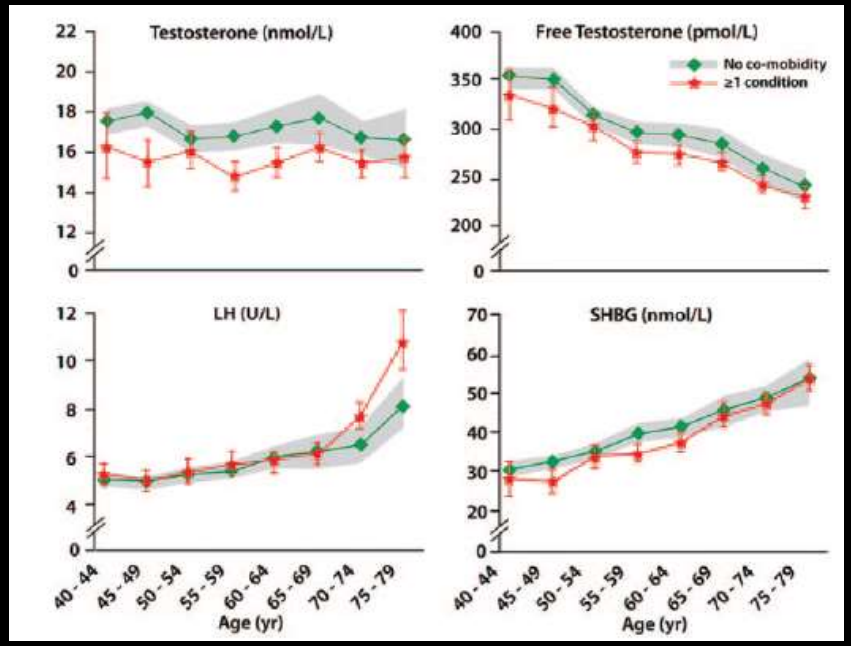
Only 25% diagnosed in life

Hypothalamic-Pituitary-Testicular Axis Disruptions in Older Men Are Differentially Linked to Age and Modifiable Risk Factors: The European Male Aging Study

Frederick C. W. Wu, Abdelouahid Tajar, Stephen R. Pye, Alan J. Silman, Joseph D. Finn, Terence W. O'Neill, Gyorgy Bartfai, Felipe Casanueva, Gianni Forti, Aleksander Giwercman, Ilpo T. Huhtaniemi, Krzysztof Kula, Margus Punab, Steven Boonen, Dirk Vanderschueren, and The European Male Aging Study Group



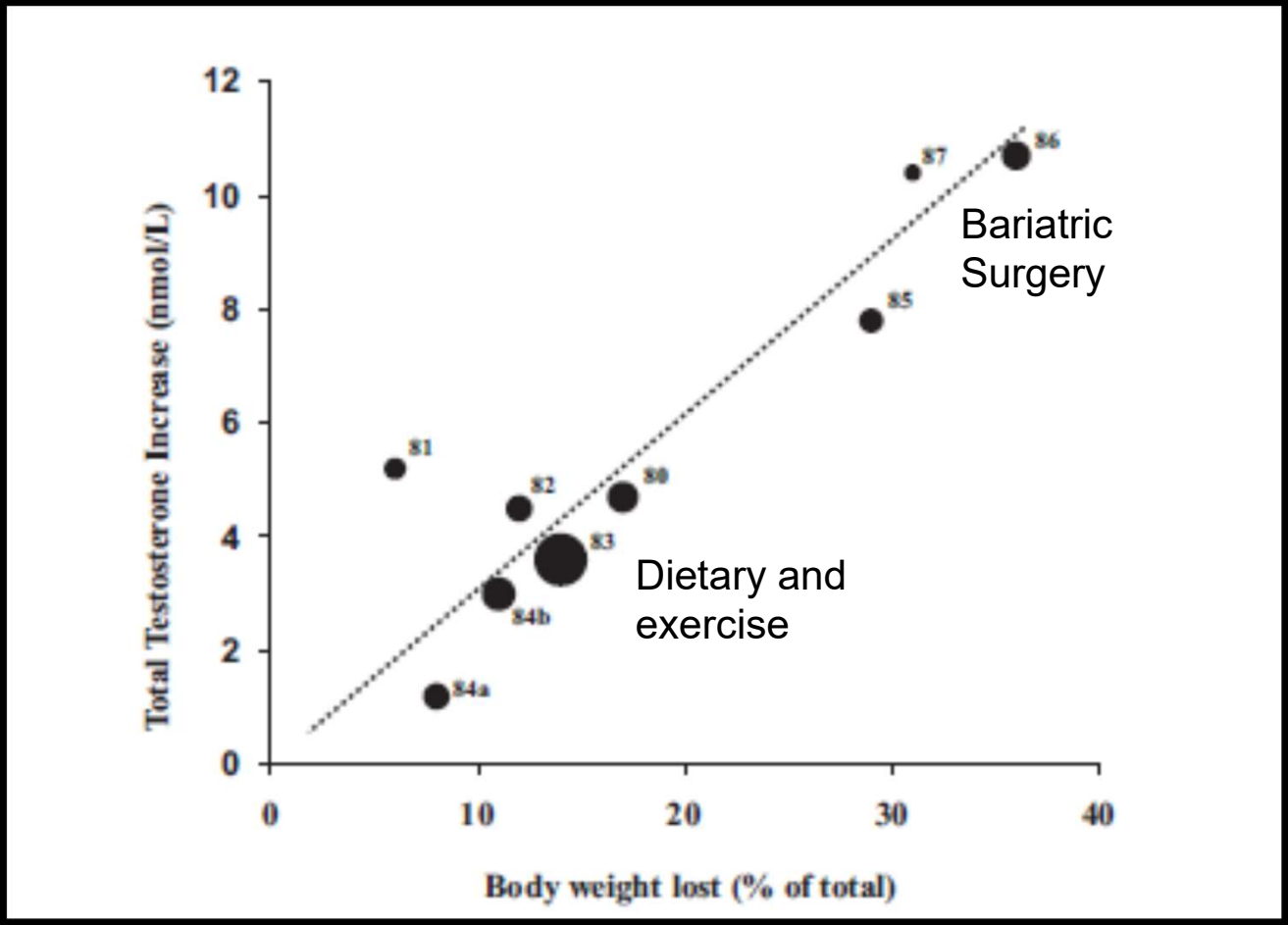
OBESITY



CO-MORBIDITIES

Wu FCW et al., JCEM 2008; 93: 2737-45

Effect of Weight Loss on Testosterone Levels



Grossman M JCEM 2011;96:2341-2353

SEXUAL HEALTH

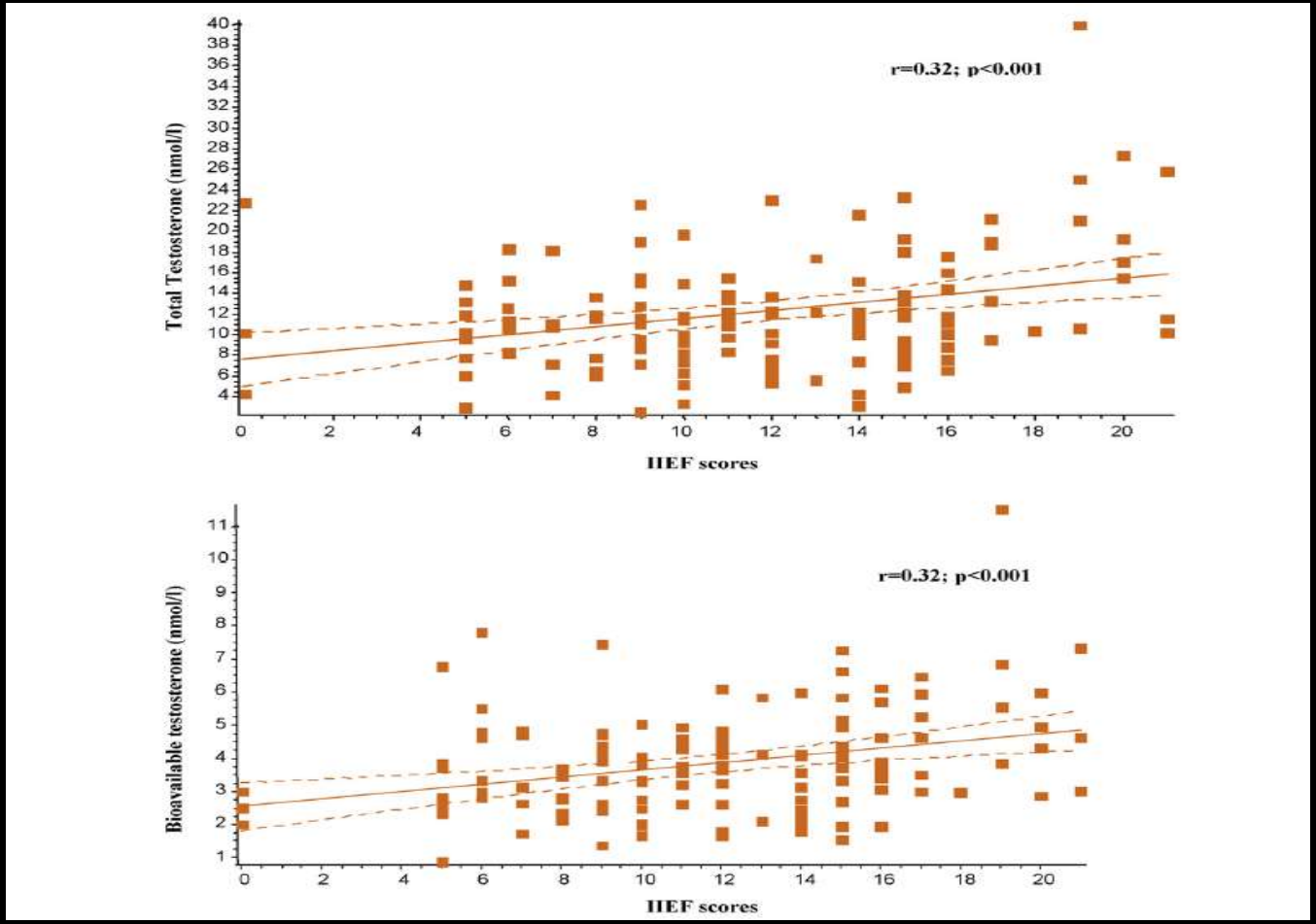
Effect of ED on Quality of Life in Men with Type 2 Diabetes

Domain	R Value	P Value
Total SF-36 Score	0.491	0.003**
Physical health	0.500	0.003**
Physical limitations	0.350	0.031*
Social	0.445	0.022*
Vitality	0.383	0.025*
Pain	0.428	0.012*
General health	0.408	0.001**

Table 6.8 - IIEF Scores versus SF-36 domains after adjusting for covariates. Only the domains that correlated significantly with IIEF scores are presented in this table. (*$p<0.05$, **$p<0.01$).

Brooke J et al. Andrology 2014;2:205-211

Association of Testosterone Levels with IIEF Scores in Men with Type 2 Diabetes



Kapoor et al, Int J Androl 2007;30:500-507

Independent Effect of Testosterone on Quality of Life in men with Type 2 diabetes and ED

All data adjusted for age, BMI, HbA1c, CVD, smoking and alcohol intake.

Brooke J et al. Andrology 2014;2:205-211

Table 1 Pearson correlations between testosterone fractions and SF-36 domains among patients with T2D and erectile dysfunction

Quality-of-life domain	Total testosterone	Bioavailable testosterone	Free testosterone
Total SF-36 score			
r	0.219**	0.199**	0.185**
p	0.001	0.004	0.007
Physical function			
r	0.224**	0.203**	0.176**
p	0.001	0.002	0.007
Physical limitation			
r	0.109	0.103	0.112
p	0.100	0.119	0.091
Emotional health			
r	0.043	0.008	0.012
p	0.513	0.898	0.856
Emotional well-being			
r	0.098	0.068	0.058
p	0.129	0.297	0.372
Social function			
r	0.205**	0.181**	0.148*
p	0.001	0.005	0.021
Vitality			
r	0.182**	0.180**	0.166*
p	0.005	0.005	0.010
Pain			
r	0.191**	0.171**	0.141**
p	0.003	0.008	0.029
General health			
r	0.186**	0.159*	0.133*
p	0.004	0.014	0.040
Health improvement			
r	0.183**	0.216**	0.223**
p	0.004	0.001	0.001

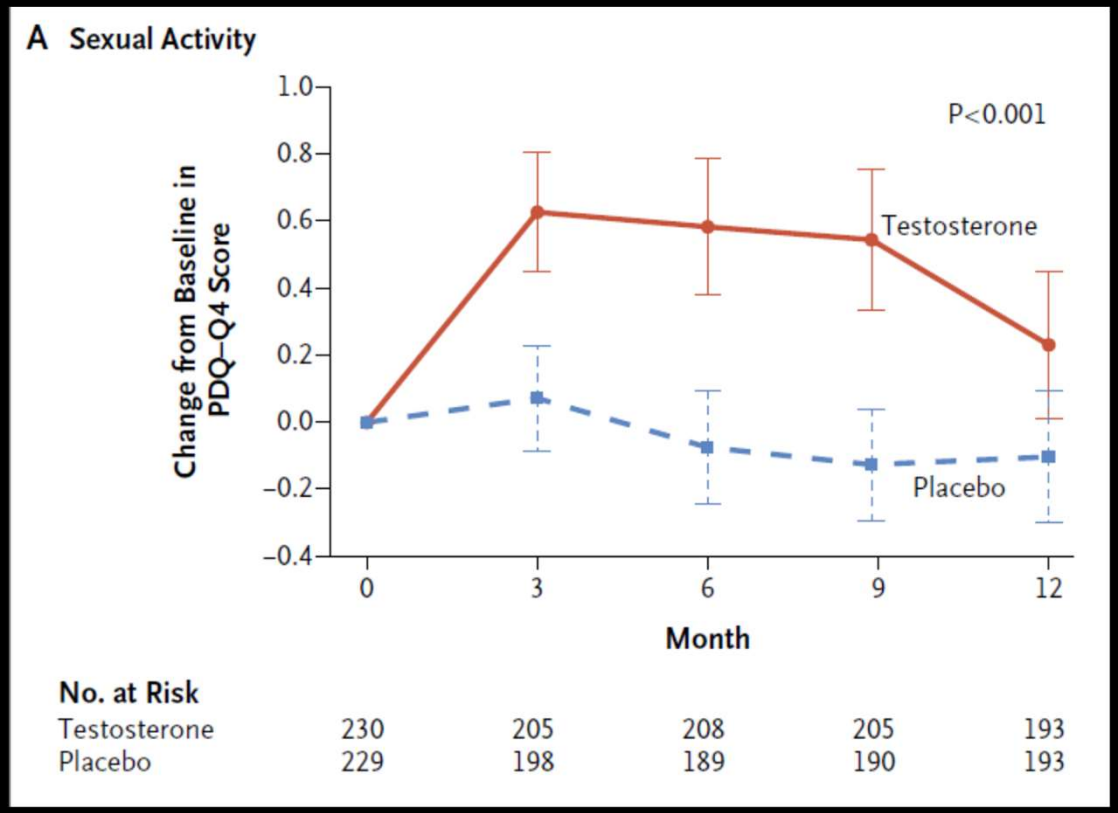
$N = 245$. *$p < 0.05$. **$p < 0.01$.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 18, 2016 VOL. 374 NO. 7

Effects of Testosterone Treatment in Older Men

P.J. Snyder, S. Bhasin, G.R. Cunningham, A.M. Matsumoto, A.J. Stephens-Shields, J.A. Cauley, T.M. Gill, E. Barrett-Connor, R.S. Swerdloff, C. Wang, K.E. Ensrud, C.E. Lewis, J.T. Farrar, D. Cella, R.C. Rosen, M. Pahor, J.P. Crandall, M.E. Molitch, D. Cifelli, D. Dougar, L. Fluharty, S.M. Resnick, T.W. Storer, S. Anton, S. Basaria, S.J. Diem, X. Hou, E.R. Mohler III, J.K. Parsons, N.K. Wenger, B. Zeldow, J.R. Landis, and S.S. Ellenberg, for the Testosterone Trials Investigators*



SEXUAL FUNCTION TRIAL

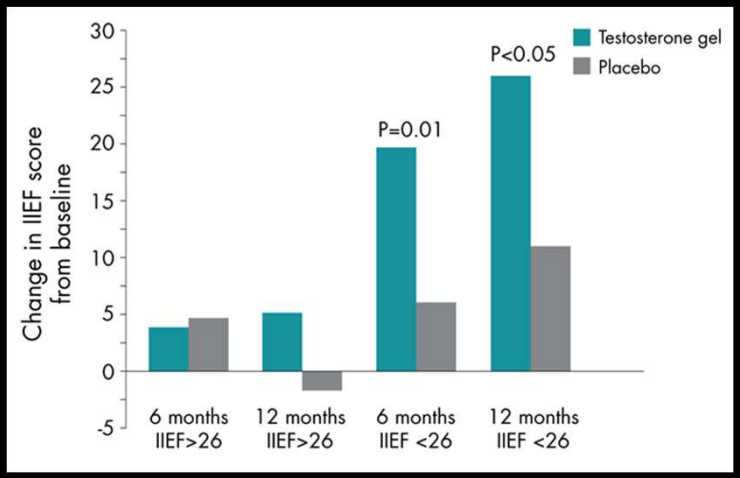
SEXUAL FUNCTION TRIAL

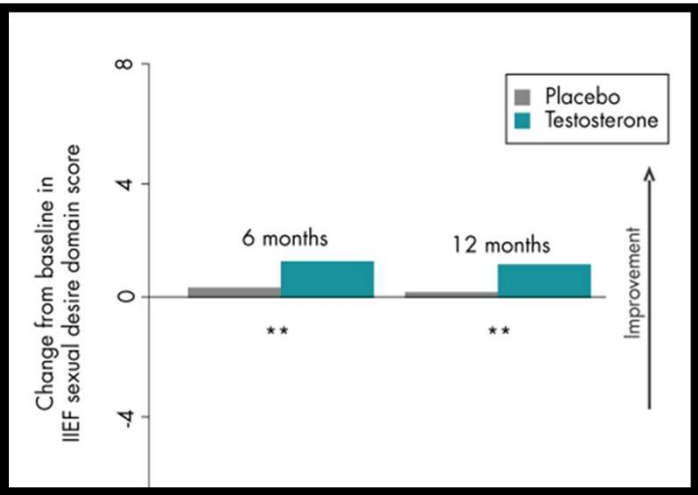
Table 1. Sexual Function Trial Outcomes.*

Cohort and Outcome	No. of Men	Baseline Value	Change from Baseline Value				Treatment Effect (95% CI)†	Effect Size (95% CI)‡	P Value§
			Month 3	Month 6	Month 9	Month 12			
Men enrolled in Sexual Function Trial									
Primary outcome: PDQ-Q4 score¶									
Testosterone	230	1.4±1.3	0.6±1.3	0.6±1.5	0.5±1.5	0.2±1.6	0.58 (0.38–0.78)	0.45 (0.30–0.60)	<0.001
Placebo	229	1.4±1.3	0.1±1.1	−0.1±1.2	−0.1±1.2	−0.1±1.4			
Secondary outcomes									
DISF-M-II sexual desire score‖									
Testosterone	234	11.9±6.7	3.5±6.3	3.5±6.0	4.0±7.4	2.6±6.5	2.93 (2.13–3.74)	0.44 (0.32–0.56)	<0.001
Placebo	236	11.6±6.6	0.7±5.8	0.8±5.6	0.9±5.5	0.0±5.0			
IIEF erectile function score**									
Testosterone	234	8.0±8.2	3.4±6.1	3.3±6.5	3.4±6.9	3.1±6.9	2.64 (1.68–3.61)	0.32 (0.20–0.44)	<0.001
Placebo	236	7.7±8.2	1.0± 5.3	0.5±6.1	0.5±7.1	1.0±6.0			
All Testosterone Trials participants††									
PDQ-Q4 score¶									
Testosterone	387	1.5±1.3	0.7±1.3	0.6±1.6	0.6±1.6	0.3±1.7	0.62 (0.45–0.79)	0.45 (0.33–0.58)	<0.001
Placebo	384	1.5±1.4	0.0±1.2	−0.1±1.3	−0.1±1.3	−0.1±1.4			

Effect of TRT on Sexual Function (IIEF) in Type 2 Diabetes

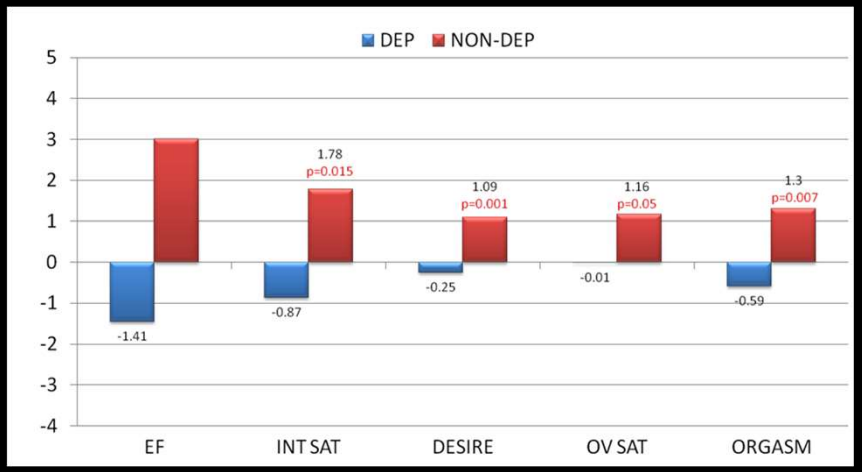
TIMES2 12 months Testosterone Gel

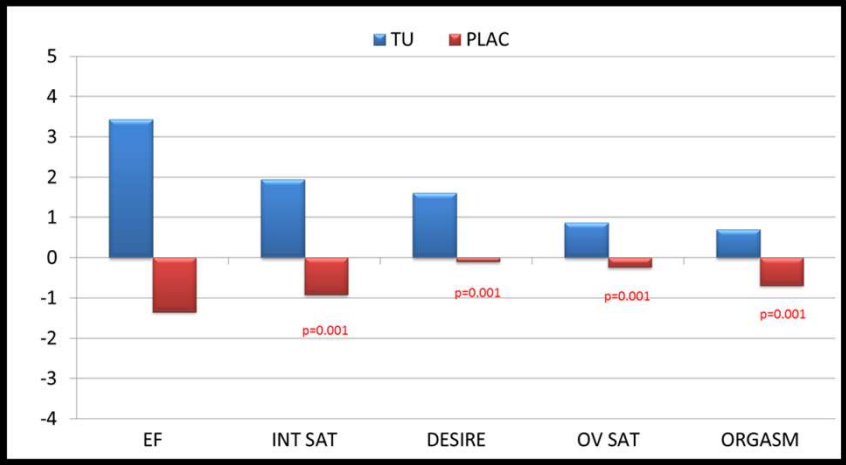




Other domains at 12 months:-
Erectile Function
p= 0.089
Intercourse satisfaction
p= 0.004
Orgasmic Function
p= 0.176
Overall sexual satisfaction
p= 0.045

BLAST 30weeks Testosterone Undeconoate i/m





Jones TH et al. Diabetes Care 2011;34:828

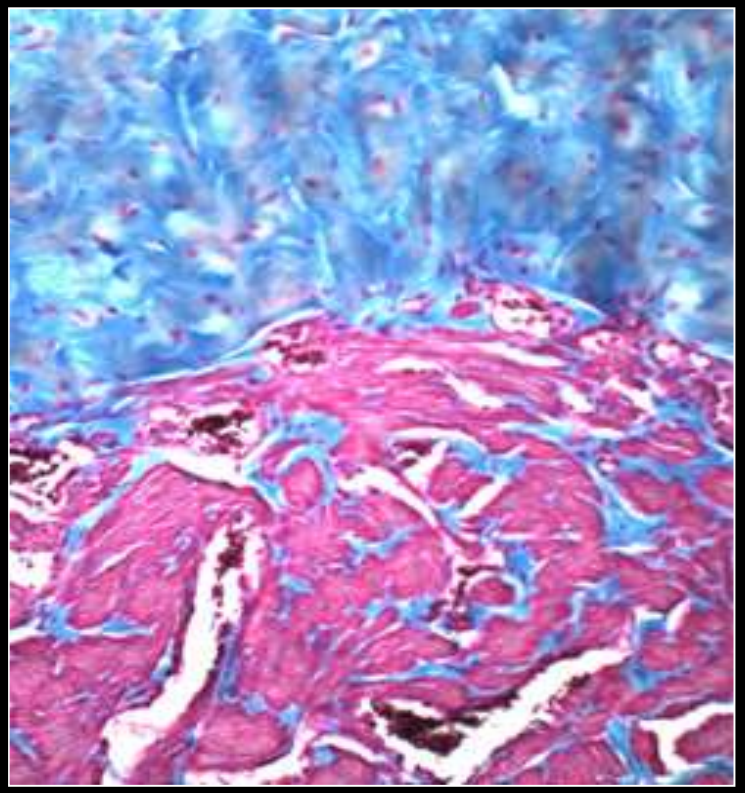
Hackett G et al. J Sex Med 2013;16:12, Hackett G et al. BJU Int 2016;118:804

Different Testosterone Levels in Diabetic Responders and Non-Responders to PDE5 Inh.

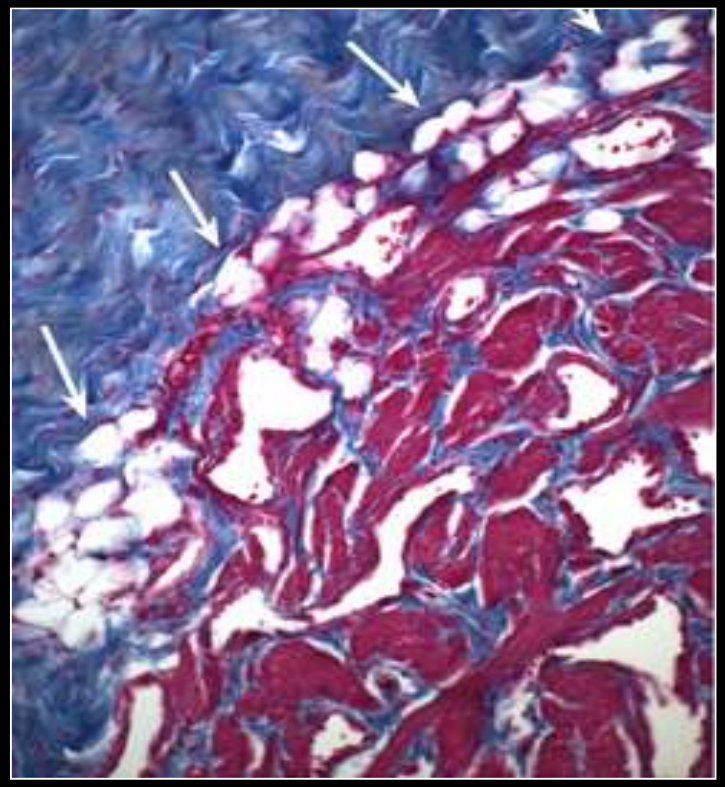
	PDE5i nonresponders n = 120	PDE5i responders n = 100	
	Mean ± SD	Mean ± SD	p value
Total testosterone (nmol/L)	**6.9 ± 1.3**	**18.6 ± 1.2**	**< 0.001**
	(4.5 - 9.6)	(14.3 - 29.1)	

Kalinchenko S et al. Aging Male 6: 94-99 (2003)

Testosterone Deprivation Promotes Adipocyte Accumulation in the Penile Corpus Cavernosum



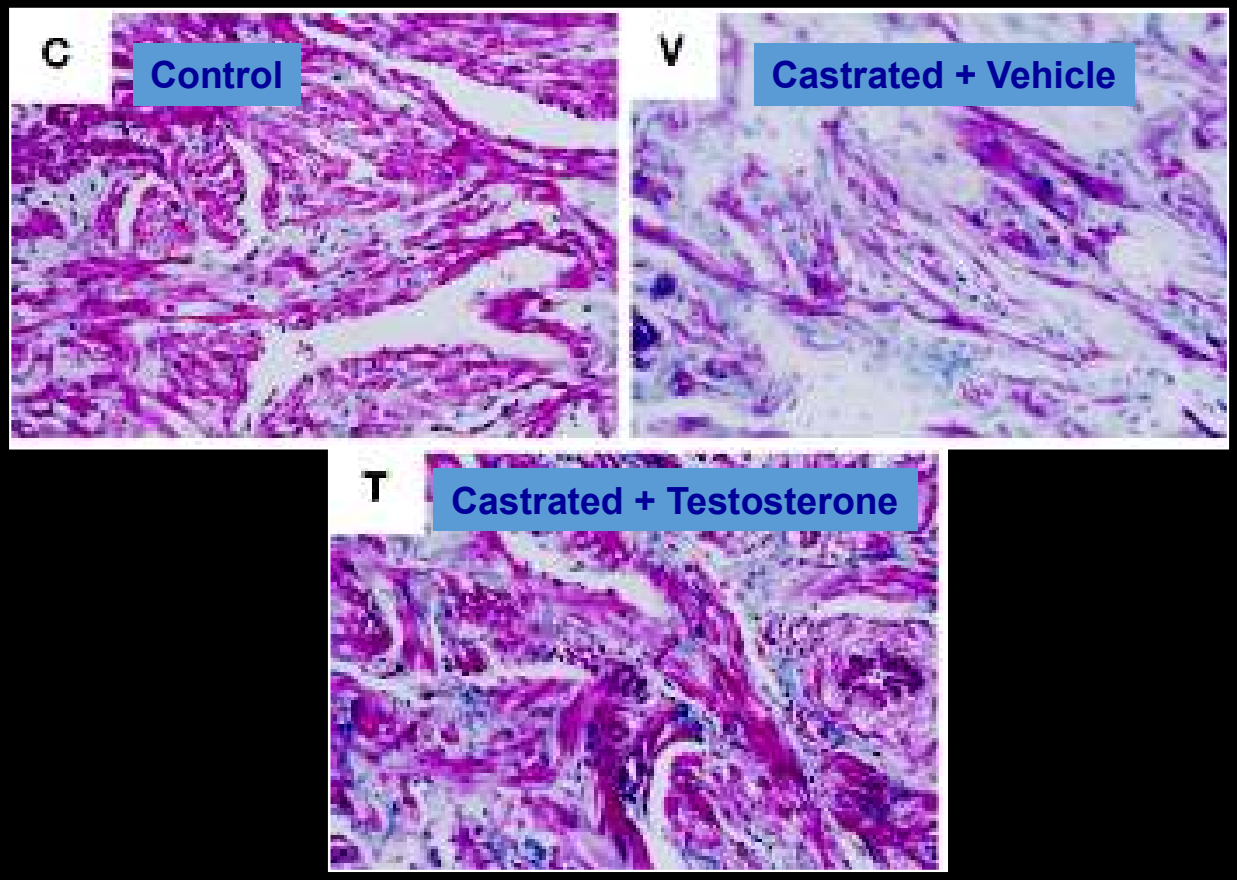
Control



Castrated

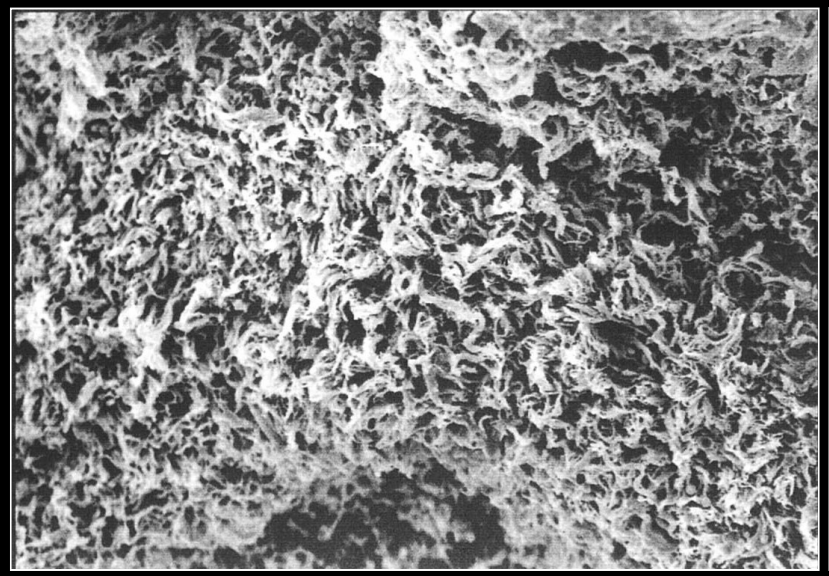
Traish A et al. J Androl 26(2): 88-94 (2005)

Effect of Castration and Androgen Substitution on Trabecular Smooth Muscle and Connective Tissue Content in the Corpus cavernosum



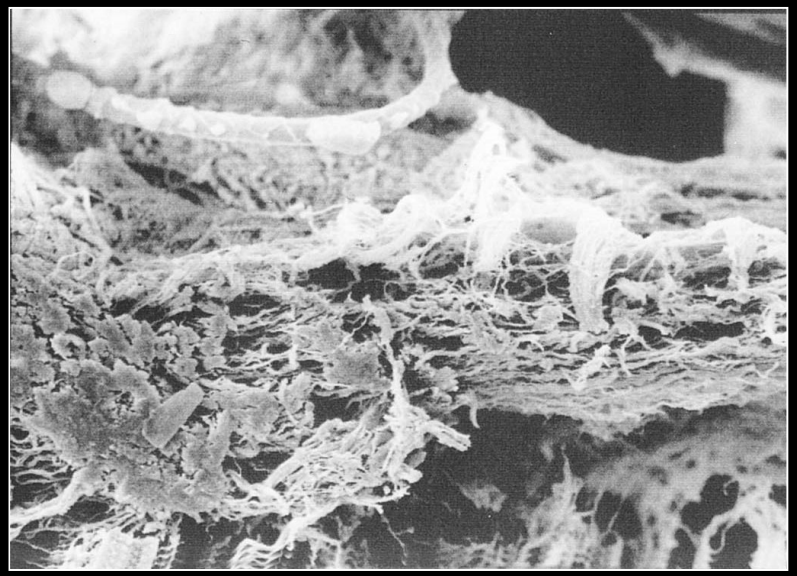
Traish A et al. Endocrinol 140(4): 1861-1868 (1999)

Effect of Androgen Deprivation on the Ultrastructure of the Tunica albuginea in Rats



Group A:

Control rich, regularly arranged elastic fibers

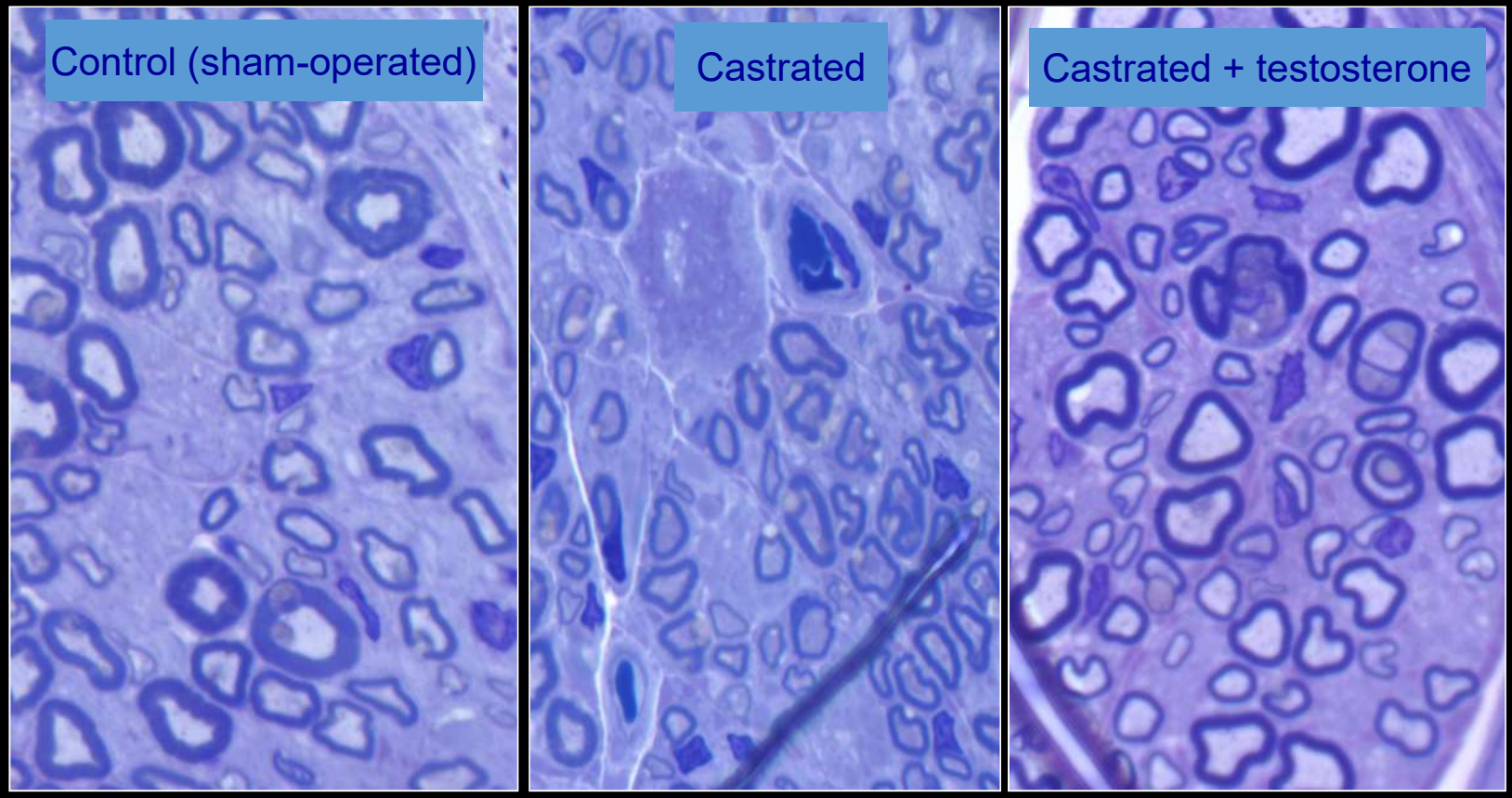


Group B:

Castrated (4 weeks) elastic fibers replaced by collagenous fibers

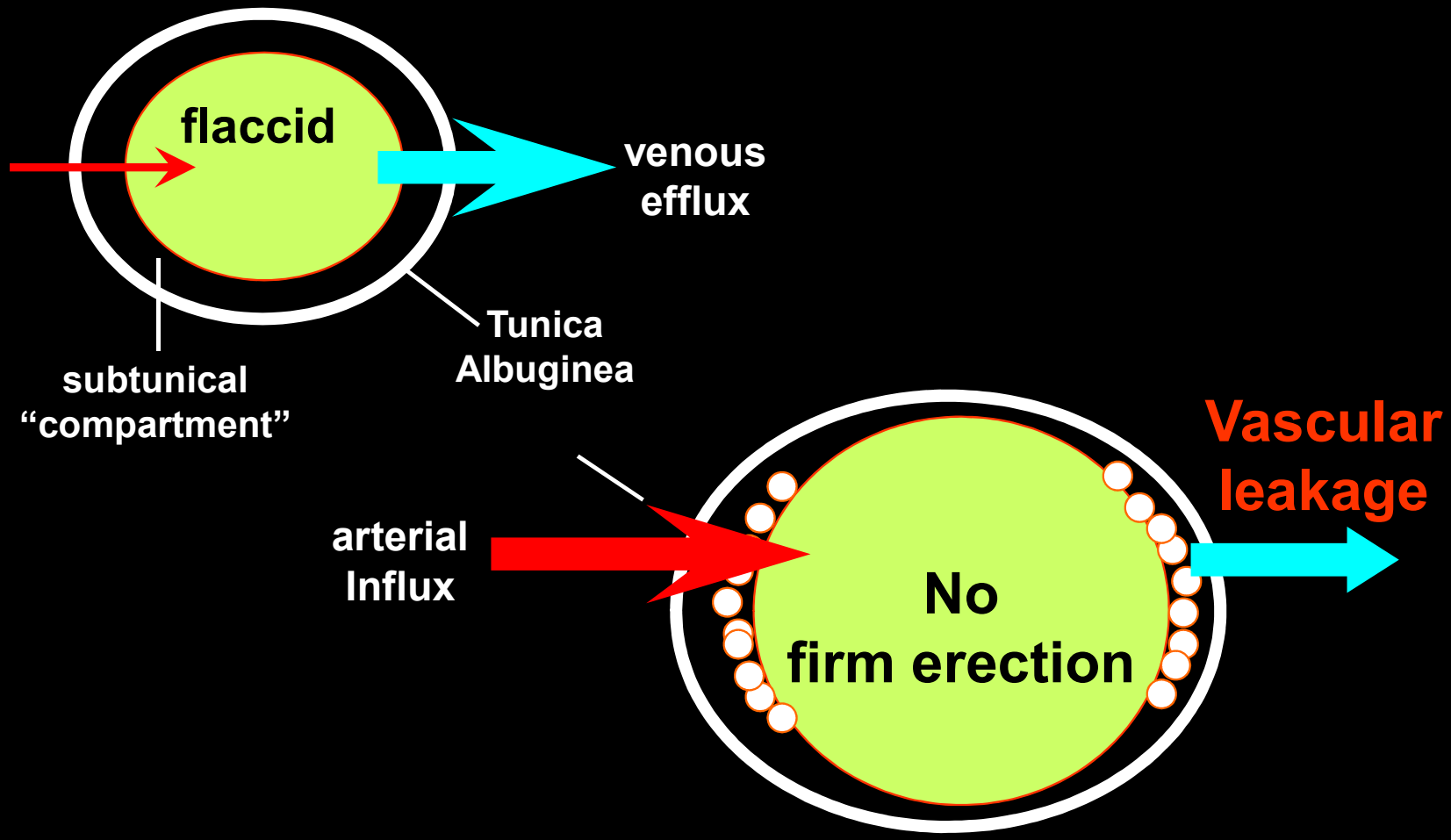
Shen Z-J Asian J Androl 1: 33-36 (2003)

Effect of Testosterone on the Cavernosal Nerve Fibers in the Rat Model

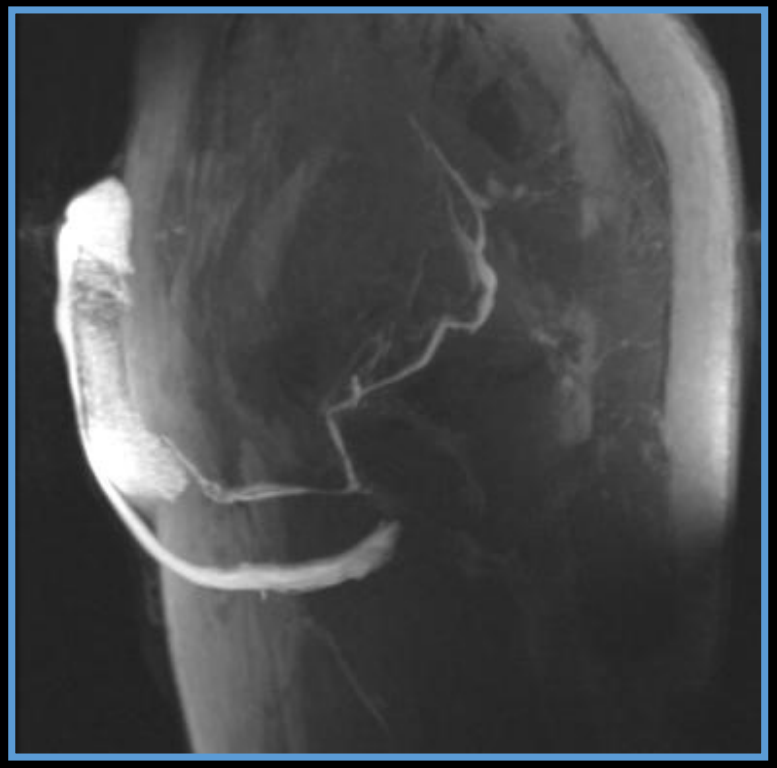


Traish A et al. Eur Urol 52: 54-70 (2007)

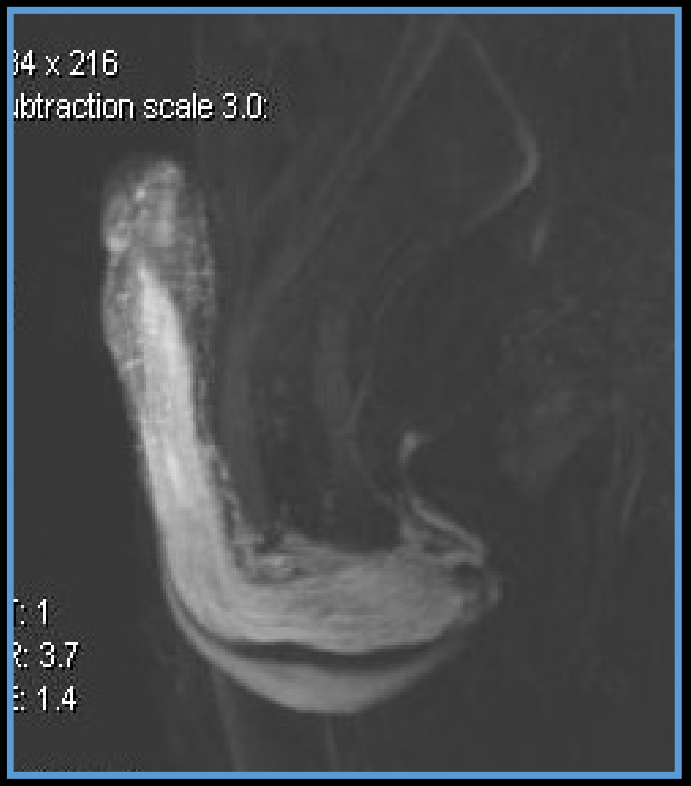
Veno-Occlusive Mechanism in Penile Erection



MRI of Venous Leak in a Hypogonadal Man before and after 21 weeks of Treatment with Nebido®



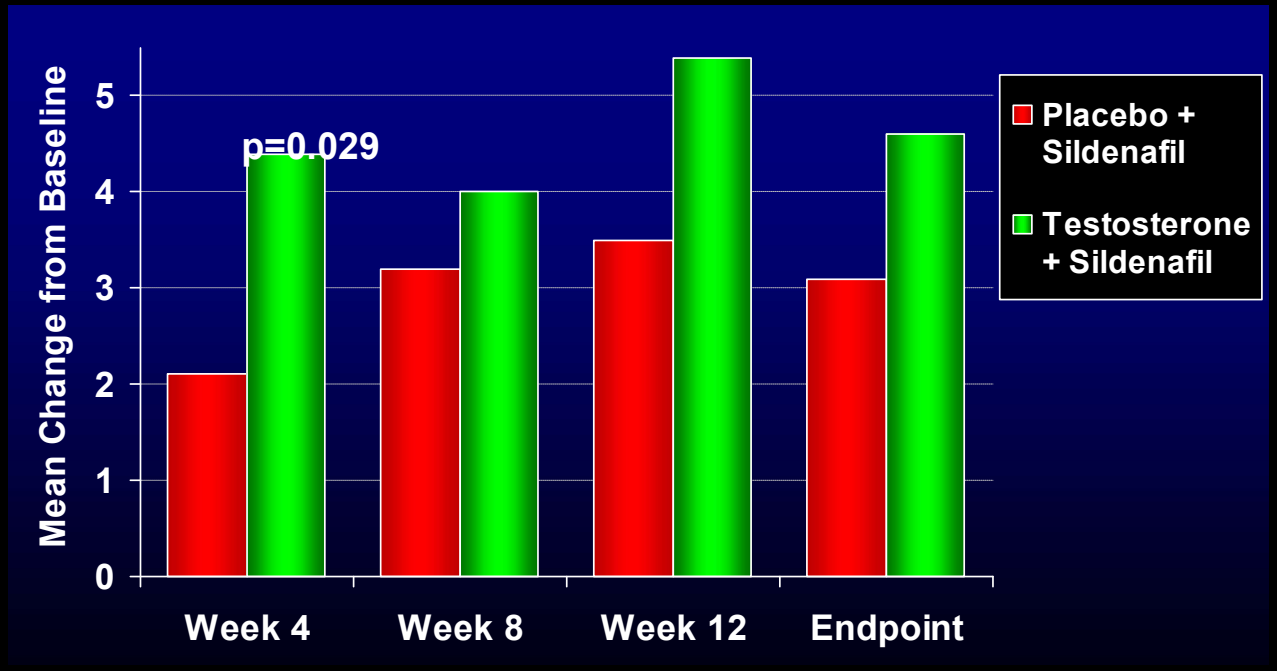
before treatment



after 21 weeks

Kurbatov D et al. Int J Impot Res, in print (2007)

12 wk Testosterone Therapy Converts Sildenafil 100 mg Non-Responders to Responders in Men with Hypogonadism (tT<14 nmol/L) and Erectile Dysfunction



IIEF Erectile Function Domain

Shabsigh R et al. J Urol 172: 658-663 (2004)

CARDIO-METABOLIC HEALTH

European Journal of Endocrinology (2006) 154 1–9 ISSN 0804-4643

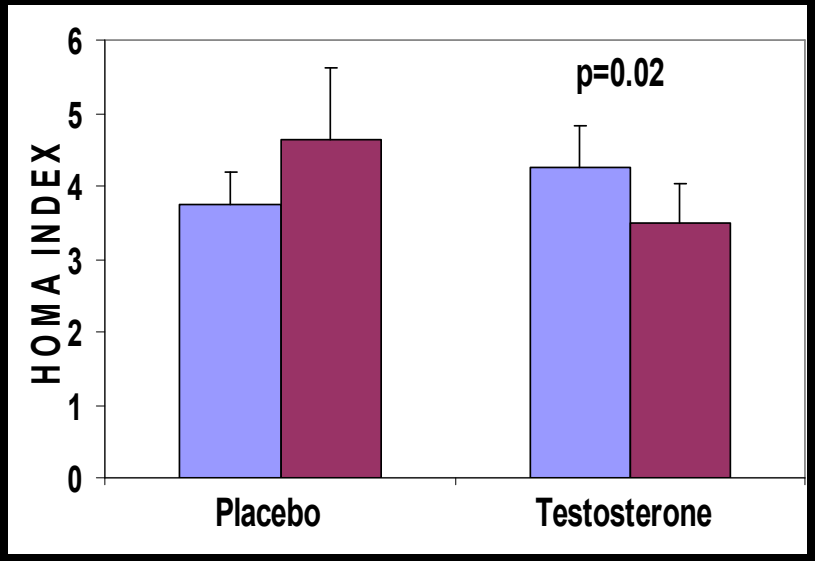
CLINICAL STUDY

Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes

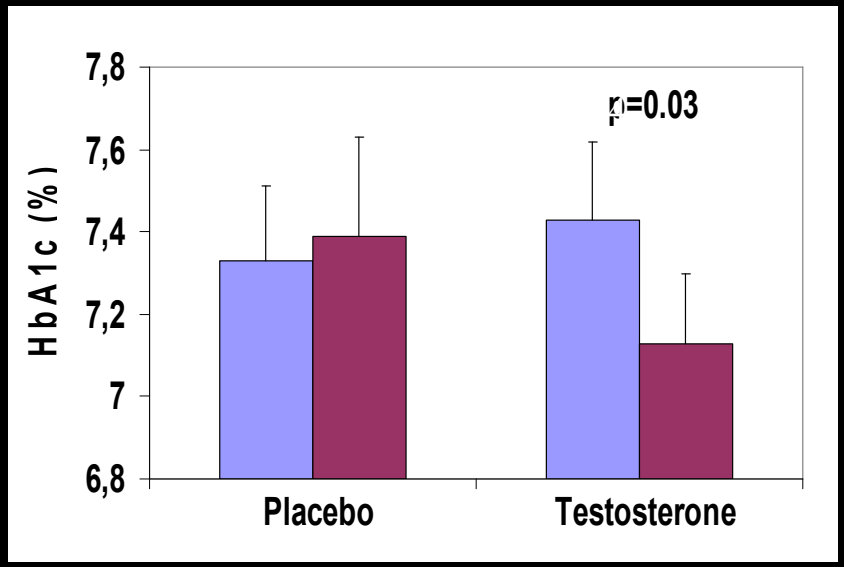
D Kapoor[1,3], E Goodwin[1], K S Channer[2] and T H Jones[1,3]

[1]*Centre for Diabetes and Endocrinology, Barnsley NHS Foundation Trust Hospital, Gawber Road, Barnsley S75 2EP, UK,* [2]*Department of Cardiology, Royal Hallamshire Hospital, Sheffield, UK and* [3]*Academic Unit of Endocrinology, Division of Genomic Medicine, University of Sheffield, UK*

(Correspondence should be addressed to T H Jones; Email: hugh.jones@bdgh-tr.trent.nhs.uk)



n=14

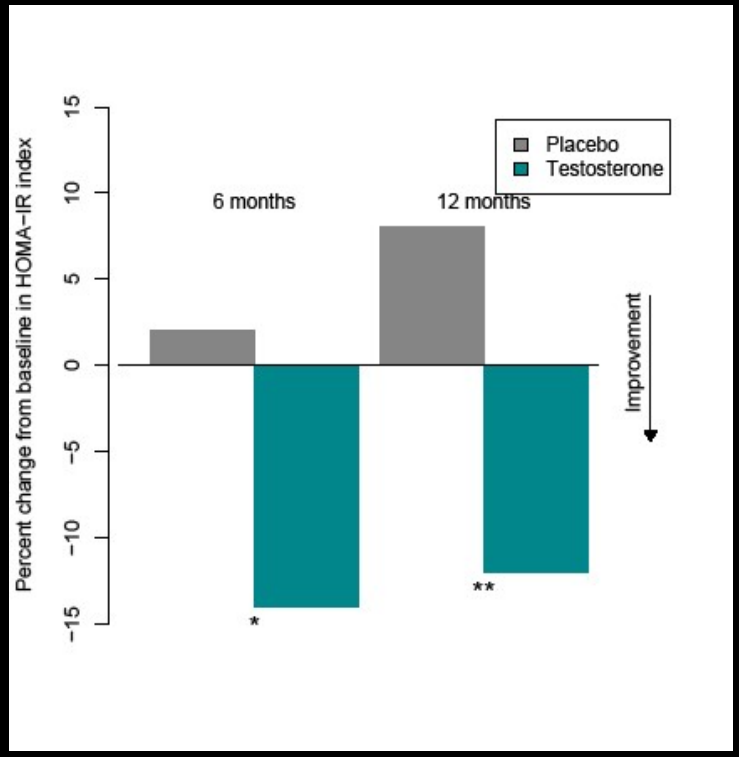


n=24

Testosterone replacement In hypogonadal men with Metabolic Syndrome and type 2 diabetes – the TIMES2 Study

Percentage mean change from baseline in HOMA-IR for patients with T2D (with or without MS) (LOCF)

RCT
Testosterone v Placebo
12 months
n=220



Jones et al. Diabetes Care 2011; 34: 828-37

EFFECT of TRT on HOMA-ir and HbA1c

TIMES2 Study

Jones TH et al
Diabetes Care
2011;34:828-837

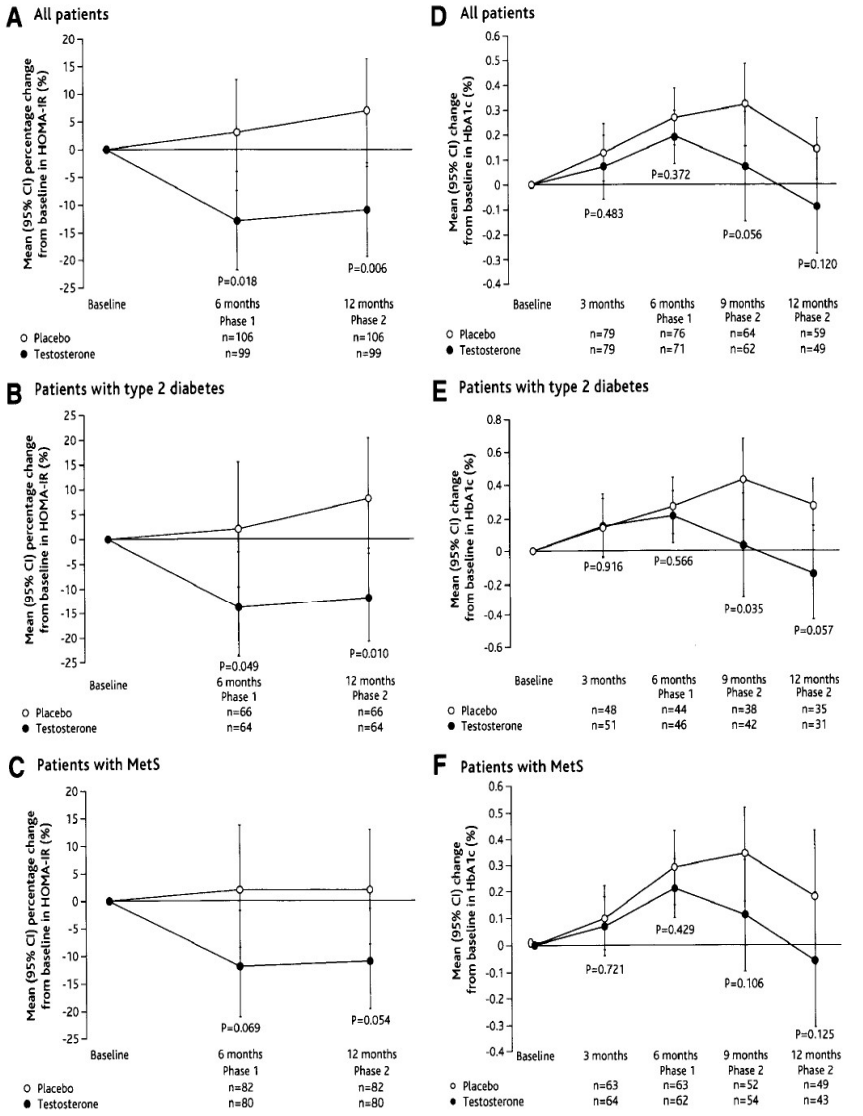
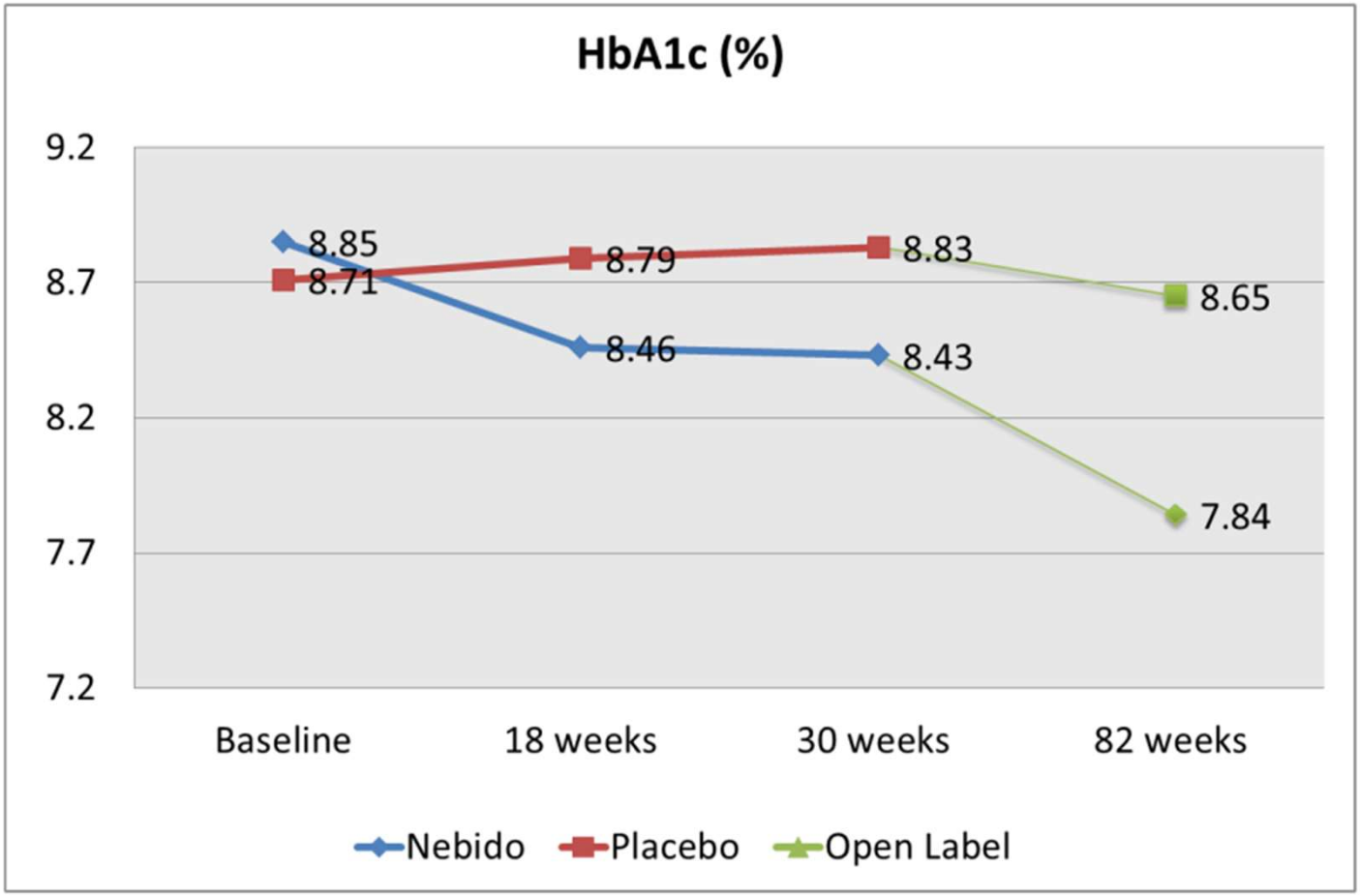
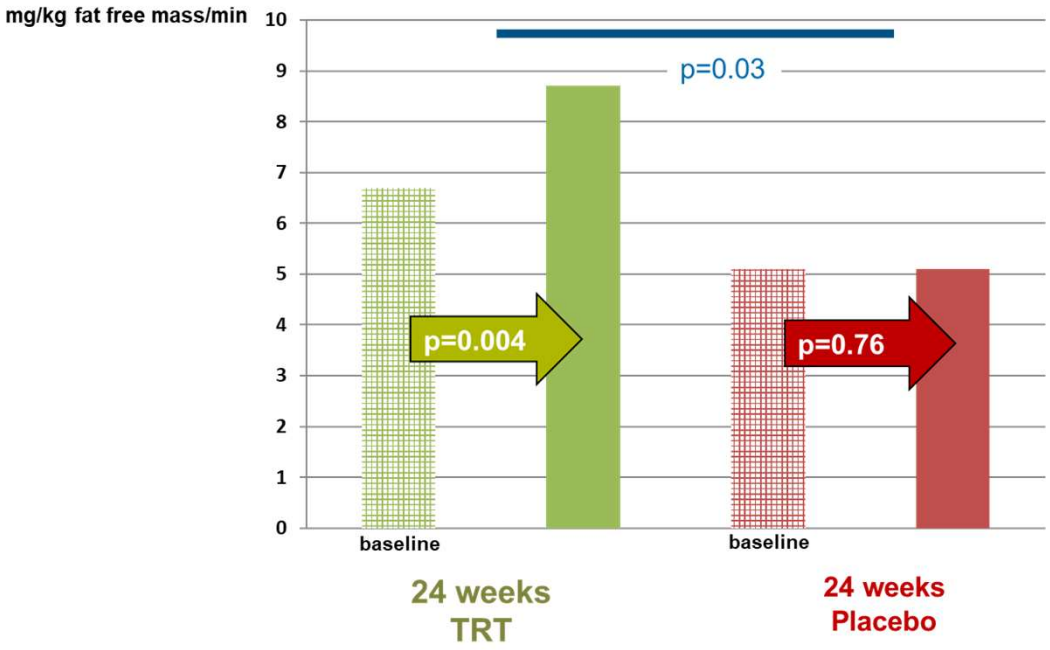


Figure 1—*Mean (95% CI) percentage change from baseline in HOMA-IR (ITT population, last observation carried forward) and change from baseline in HbA_{1c} (ITT population, study completers) among all patients (A and D), patients with type 2 diabetes (B and E), and patients with MetS (C and F). P values reported for comparisons between groups.*

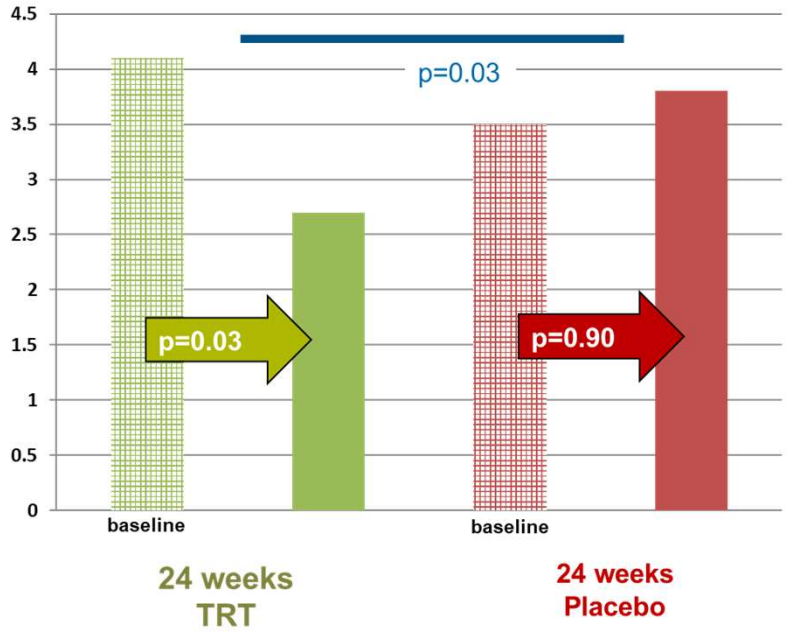
HbA1c Open Label – Poorly Controlled Patients (N=45)



Effect of Testosterone on Insulin Resistance Hyperinsulinaemic Euglycaemic Clamp & HOMA-ir



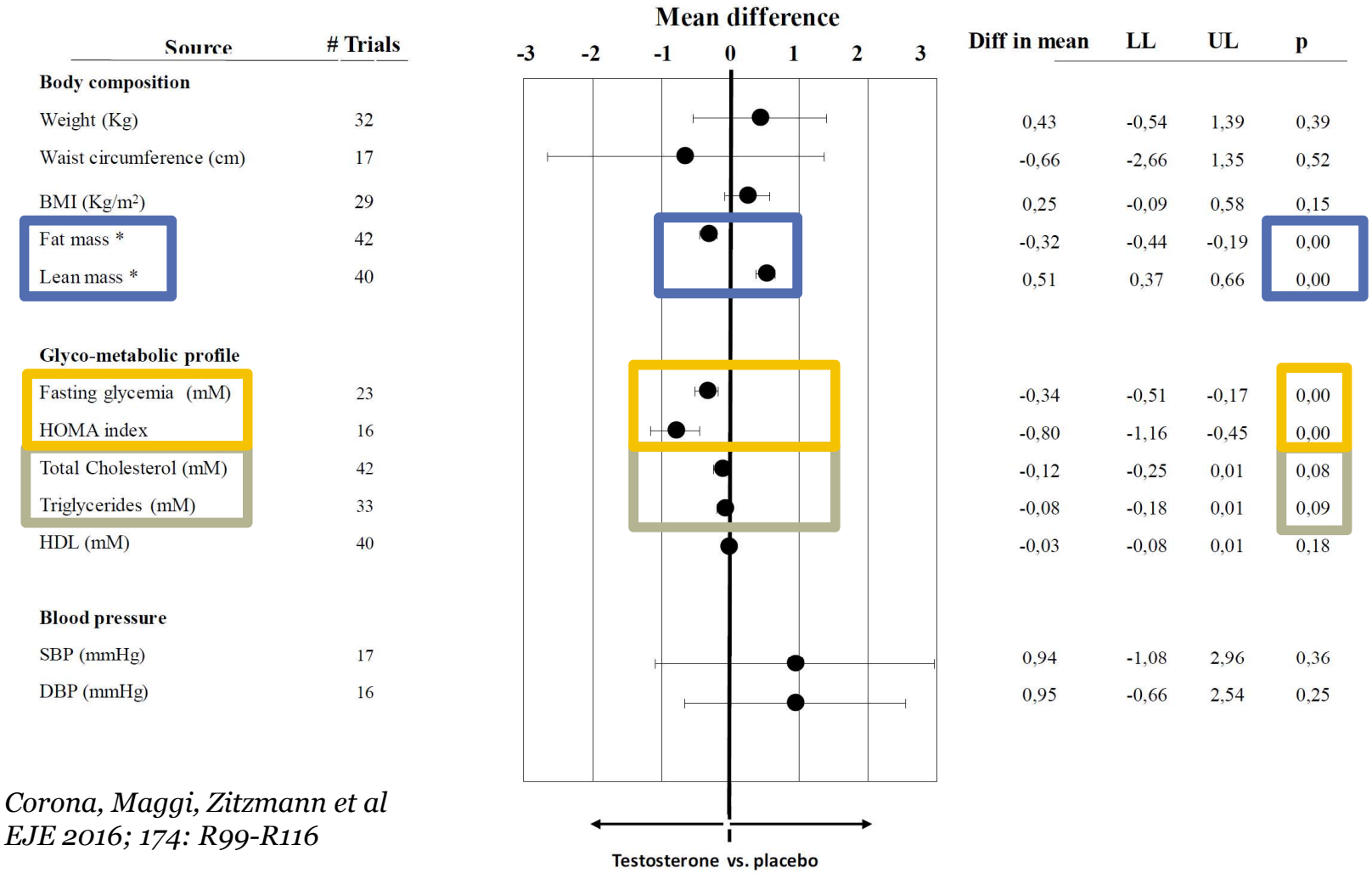
Dhindsa et al Diabetes Care 2016 39:1-10



Dhindsa et al Diabetes Care 2016 39:1-10

Meta-Analysis of 59 randomized controlled trials of T substitution in hypogonadism

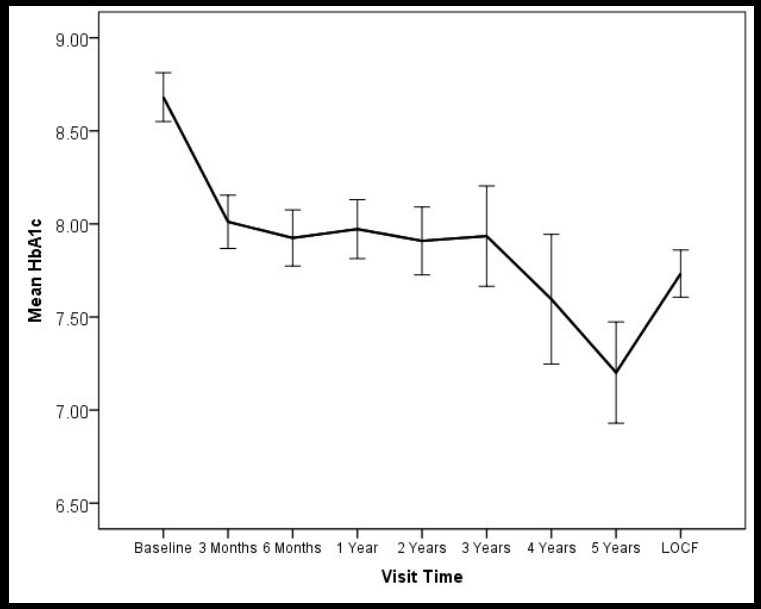
3029 men (treated) vs 2049 (controls)



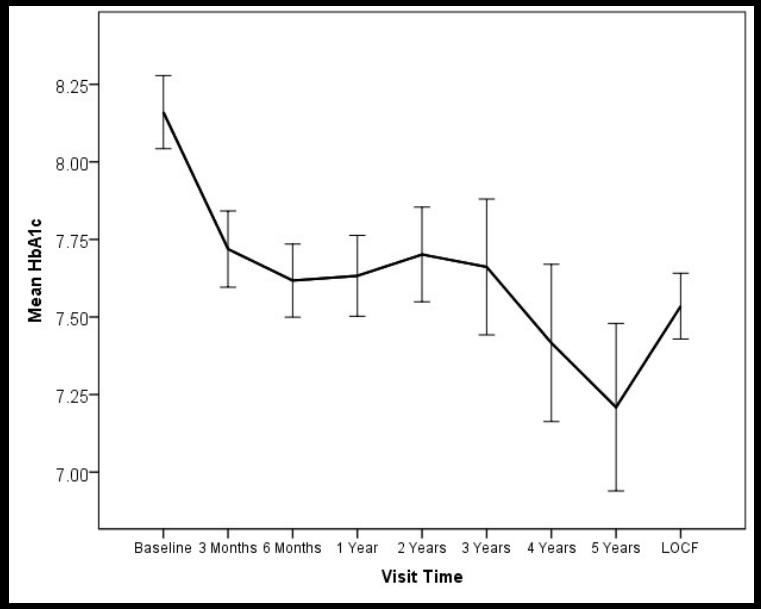
Corona, Maggi, Zitzmann et al
EJE 2016; 174: R99-R116

Effect of TRT on HbA1c in Uncontrolled Type 2 Diabetes in Routine Clinical Practise

HbA1c >7% at baseline
n=104



HbA1c >6.5% at baseline
n=140

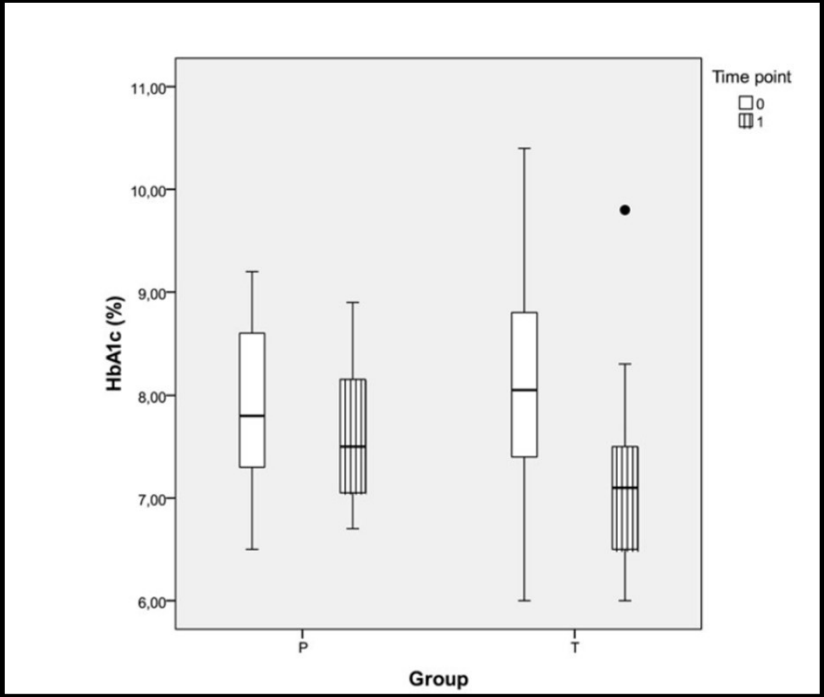


STRIDE Study: Study of Testosterone Replacement In Diabetic mEn

- Randomised double-blinded placebo-controlled add-on of testosterone therapy (depot testosterone undecanoate 6 weekly followed by 3 monthly injections) in hypogonadal men with poorly controlled T2D HbA1c >7%
- Phase 1 – 6 month RCT
- Phase 2 - 6 month open-label
- Primary Outcome – HbA1c
- N=78

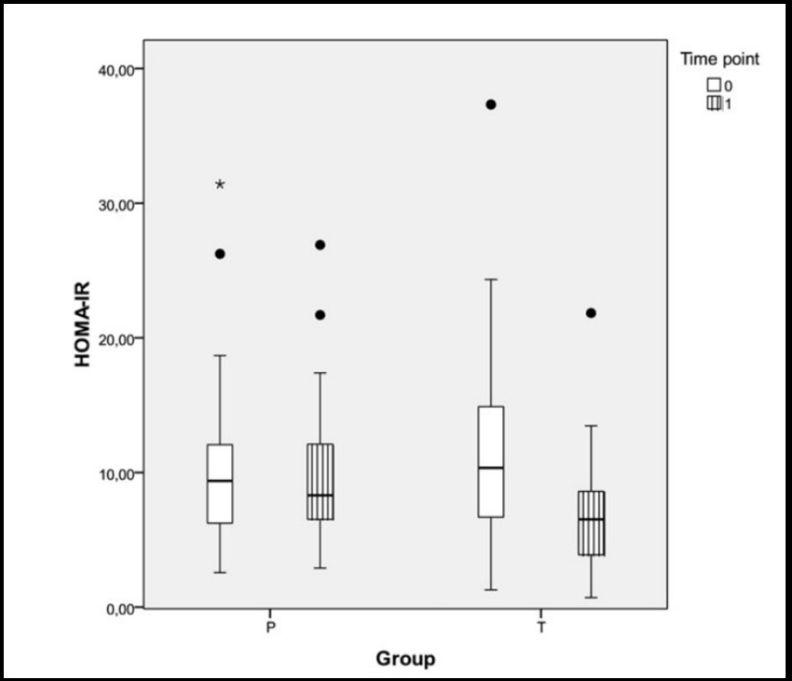
Effect of Testosterone Undeconoate on HbA1c and HOMA-IR in Type 2 Diabetes Mellitus
Randomised Placebo Controlled Trial (n=55, T=28, P=27)

HbA1c



HbA1c ↓0.94±0.88% p<0.001

Homa-ir

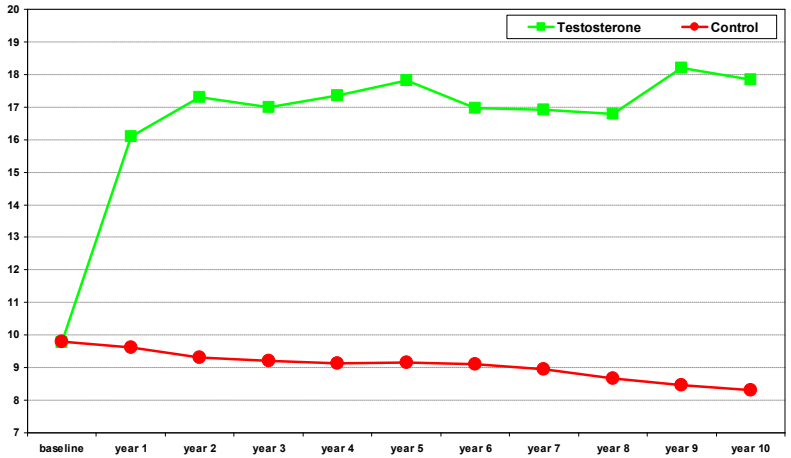


HOMA-ir ↓4.64±4.25 p<0.001

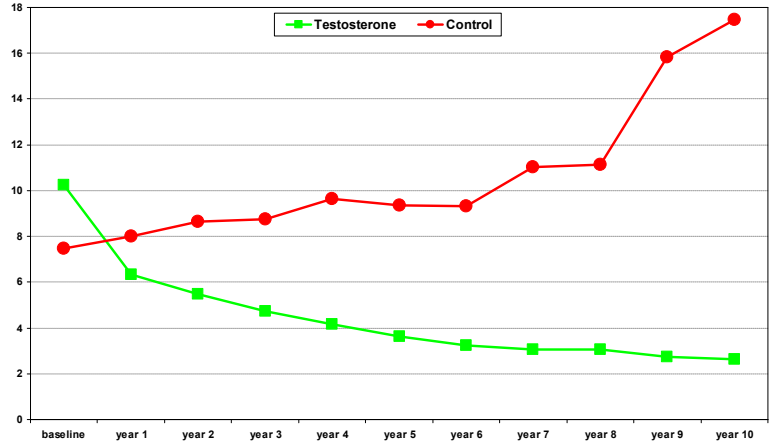
Groti K et al. Aging Male 2018; DOI.org/10.1080/13685538.2018.1468429

Registry Study - Improvement of Type 2 Diabetes (T2DM) in Hypogonadal Men with Long-Term Testosterone Therapy (TTh) is Sustained for up to 10 Years Compared (N=141)to Untreated Controls (n=170)

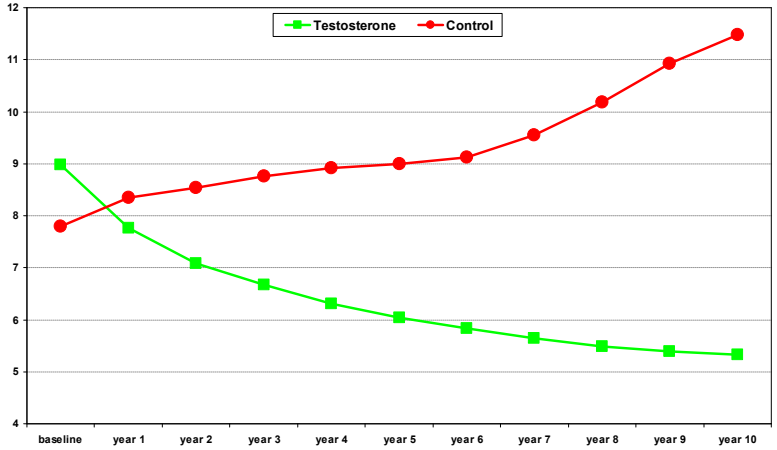
TESTOSTERONE



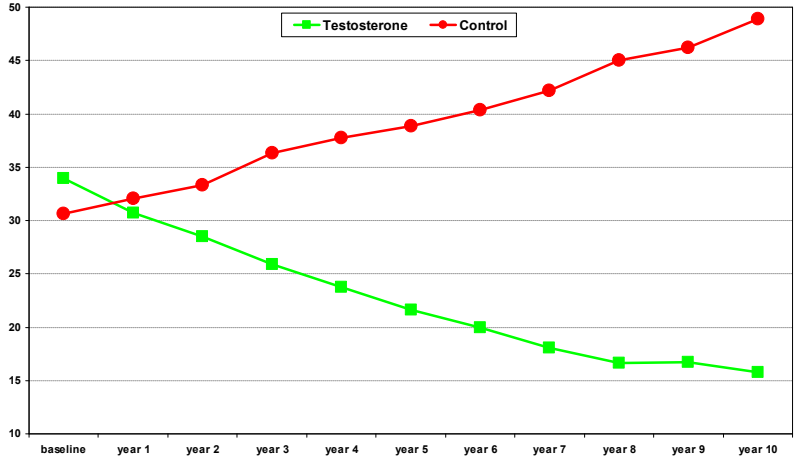
HOMA-ir



HbA1c



INSULIN DOSE U/DAY

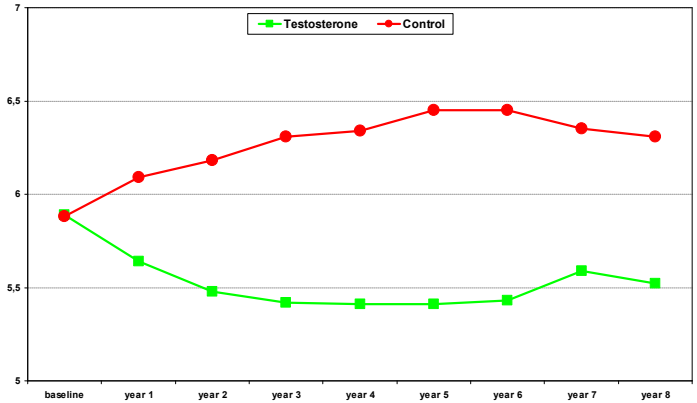


Data adjusted for weight, WC, FBG, Syst & Diast BP, lipid profile, QOL *=p<0.0001

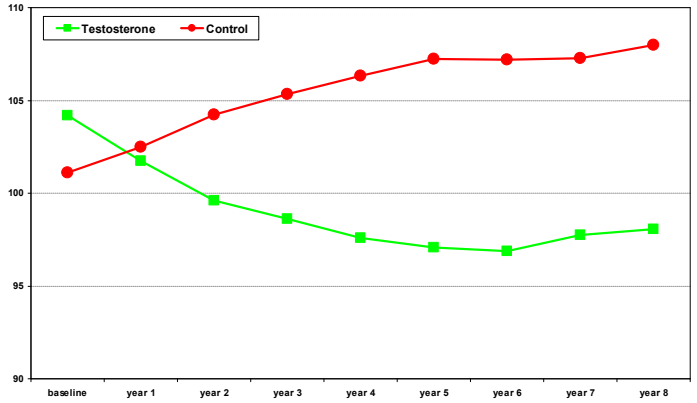
Wissinger U et al. Diabetologia 61 (Suppl. 1): S328 (2018)

Progression from Prediabetes to Type 2 Diabetes (T2DM) in 303 Hypogonadal Men with (n=220) and without (n=83) Testosterone Treatment:8-Year Real-Life Data from a Registry

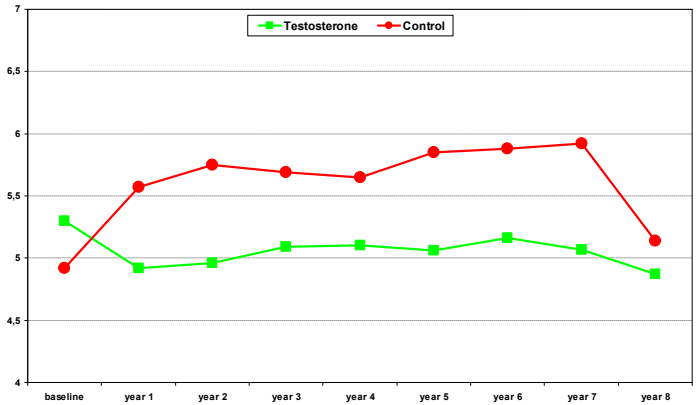
HbA1c %



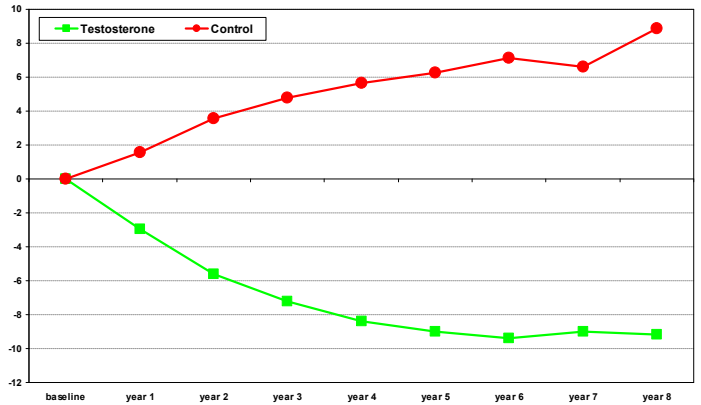
Waist Circumference (cm)



FB Glucose mmol/l

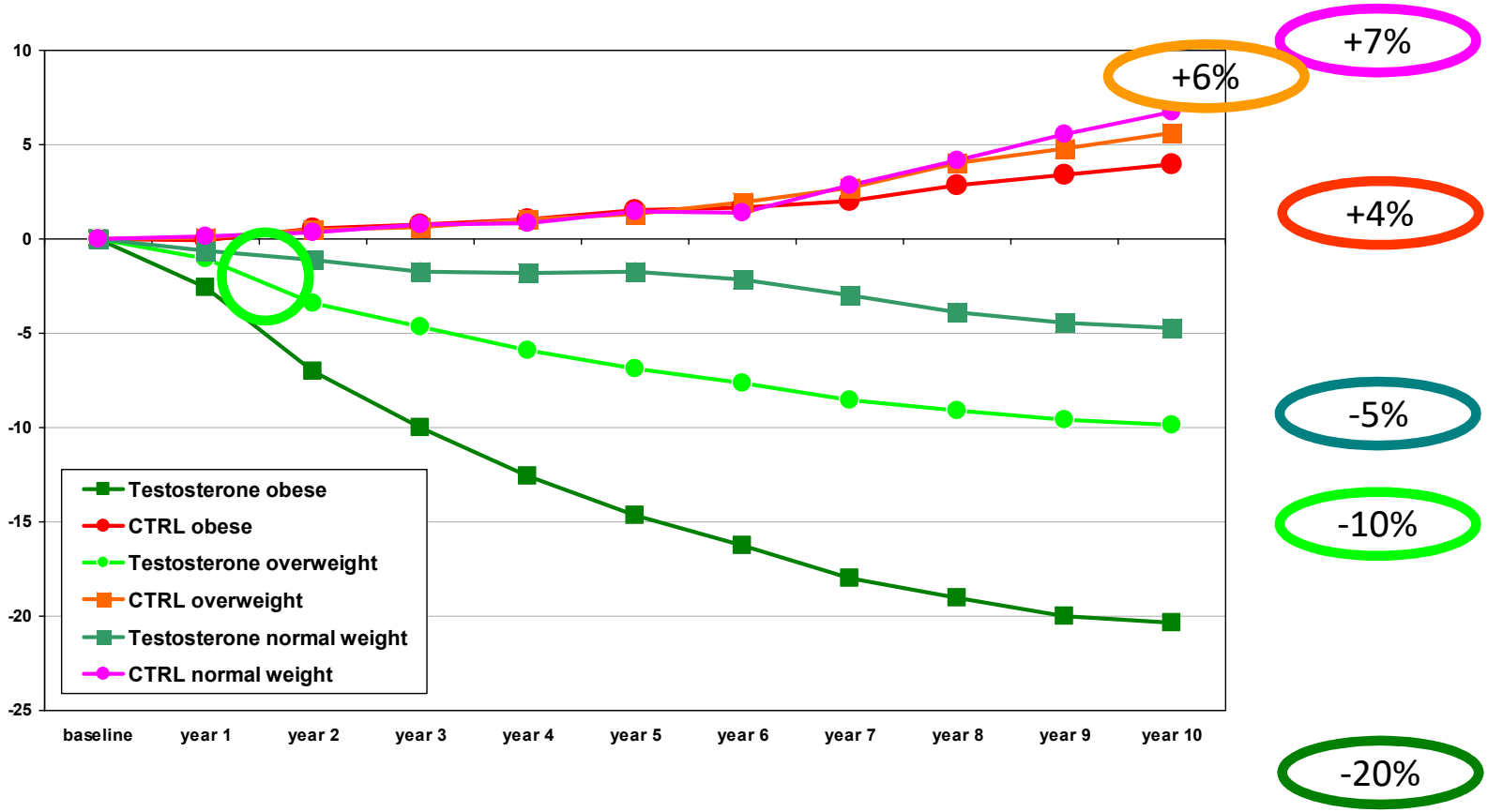


Weight (kg)

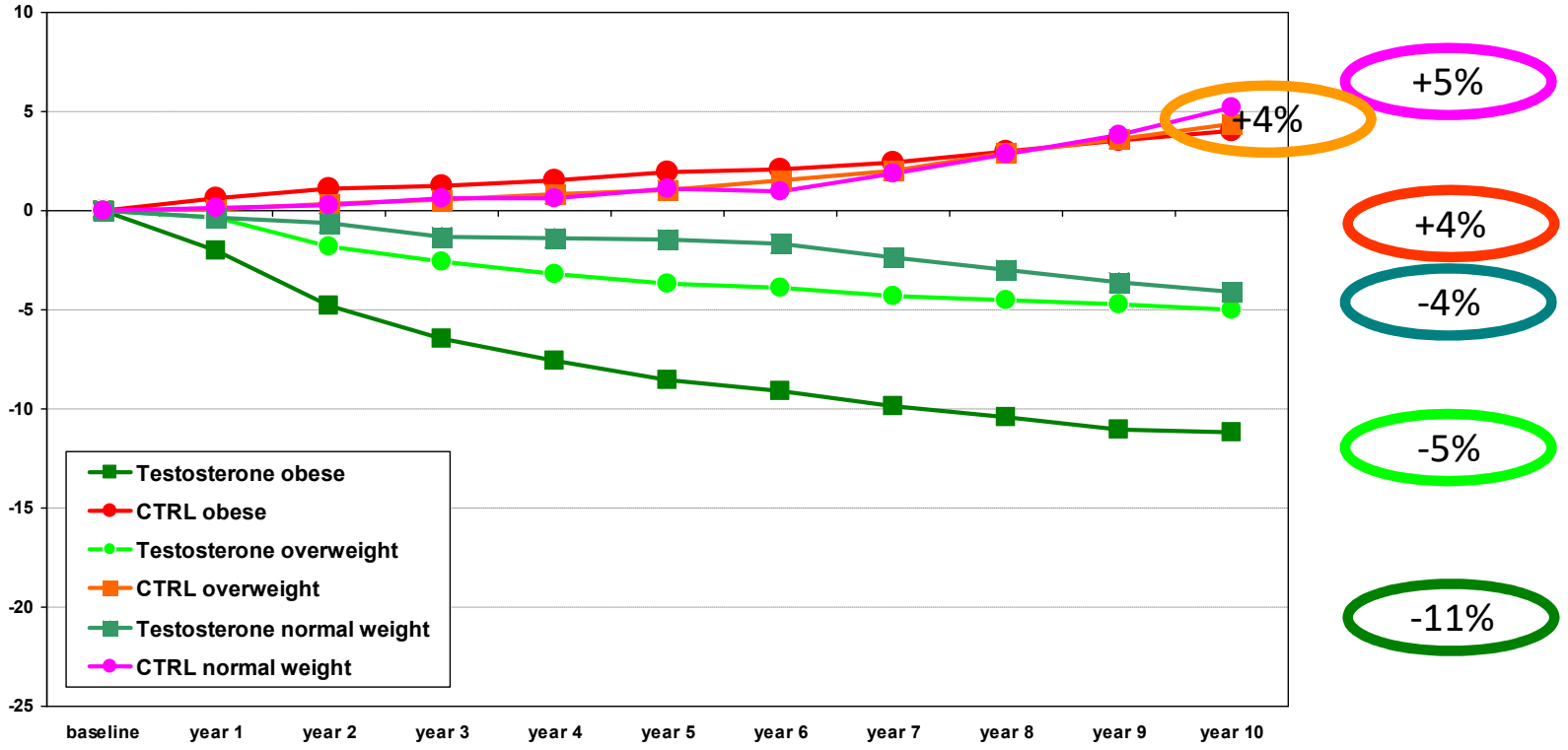


#adjusted for waist circumference, weight, fasting glucose, systolic and diastolic blood pressure, total cholesterol, HDL, LDL, triglycerides, AMS

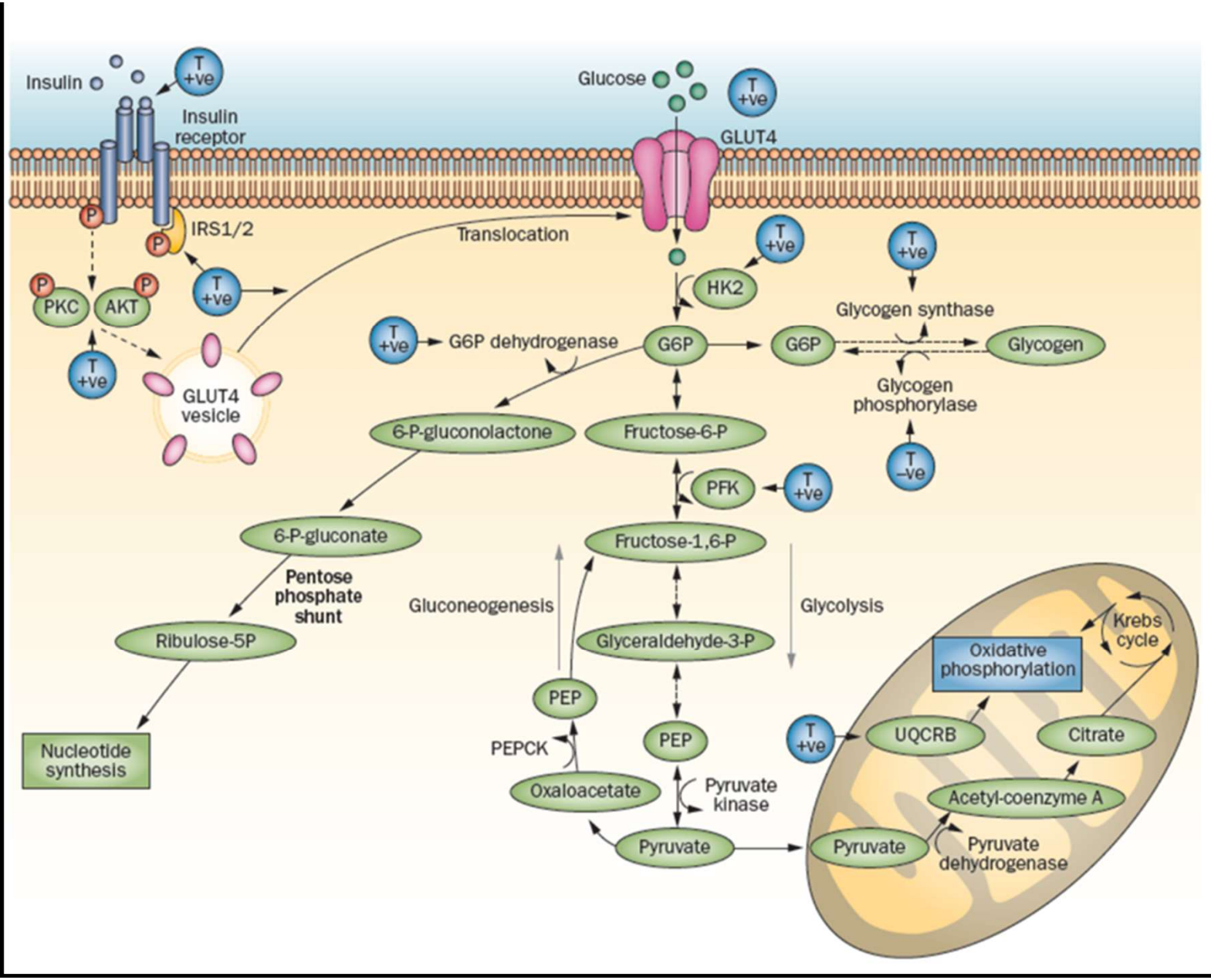
Model-Adjusted Mean Weight Change (%) in 805 Hypogonadal Men with Normal Weight, Overweight, and Obesity



Model-Adjusted Mean Change in Waist Circumference (%) in 805 Hypogonadal Men with Normal Weight, Overweight, and Obesity



Glucose Uptake and Utilisation



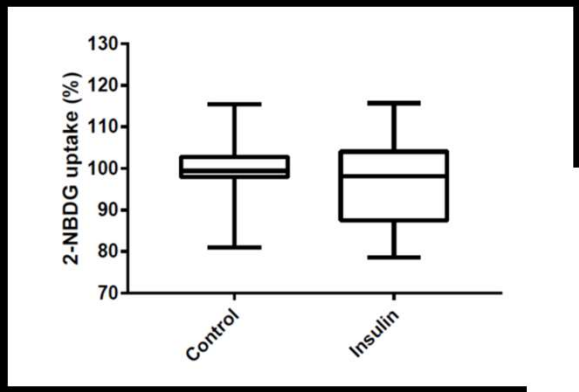
Rao P et al. Nature Rev Endocrinol 2013;9:479

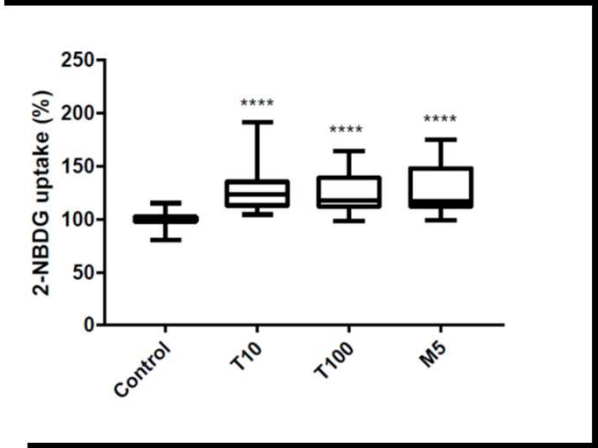
Kelly DM, Jones TH J Endocrinol 2013;217:R25-R45

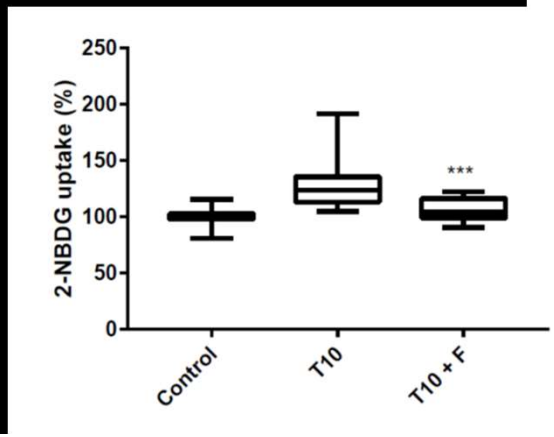
Kelly M et al. Endocrine 2016;54:504

Testosterone – Glucose Uptake and Utilisation

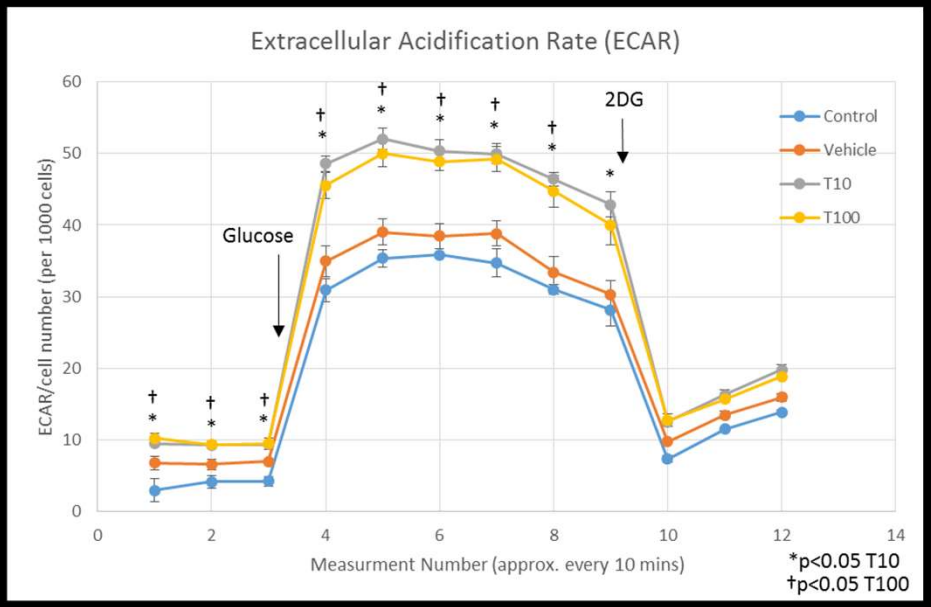
EFFECT OF TESTOSTERONE ON GLUCOSE UPTAKE IN HEPG2 INSULIN RESISTANT HUMAN LIVER CELLS



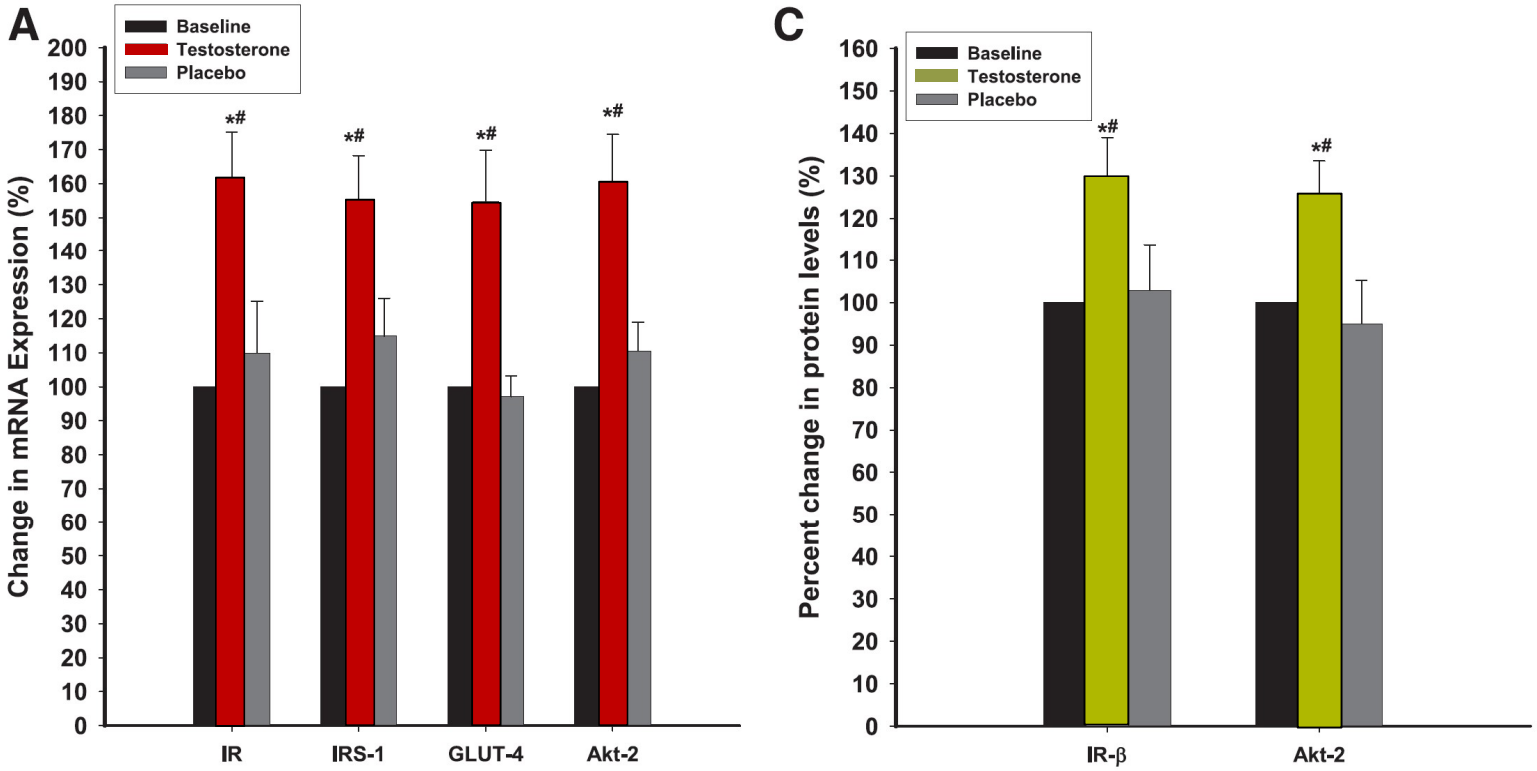




Effect of Testosterone on Glycolytic Rate



Functional background:
Genetic changes induced by TRT



Percent change in mRNA expression or protein levels of insulin signaling mediators in adipose tissue after 24 weeks of testosterone or placebo treatment

Dhindsa et al Diabetes Care 2016 39:1-10

European Heart Journal Advance Access published August 6, 2015

European Heart Journal
doi:10.1093/eurheartj/ehv346

FASTTRACK CLINICAL RESEARCH
Coronary artery disease

Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men

Rishi Sharma[1], Olurinde A. Oni[1], Kamal Gupta[2], Guoqing Chen[3], Mukut Sharma[1], Buddhadeb Dawn[2], Ram Sharma[1], Deepak Parashara[2,4], Virginia J. Savin[5], John A. Ambrose[6], and Rajat S. Barua[1,2,4]*

[1]Division of Cardiovascular Research, Kansas City VA Medical Center, Kansas City, MO, USA; [2]Division of Cardiovascular Diseases, University of Kansas Medical Center, Kansas City, KS, USA; [3]Division of Health Services Research, University of Kansas Medical Center, Kansas City, KS, USA; [4]Division of Cardiovascular Medicine, Kansas City VA Medical Center, 4801 E. Linwood Boulevard, Kansas City, MO 64128, USA; [5]Division of Nephrology, Kansas City VA Medical Center, Kansas City, MO, USA; and [6]Division of Cardiovascular Medicine, University of California San Francisco, Fresno, CA, USA

Received 2 June 2015; revised 1 July 2015; accepted 6 July 2015

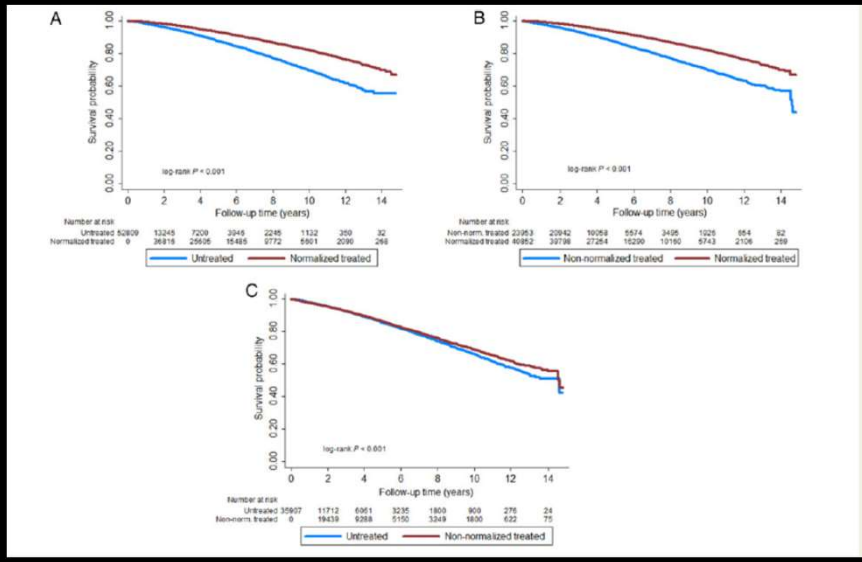
Sharma R et al. Eur Heart J, published online August 06, 2015; doi: 10.1093/eurheartj/ehv346

Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men

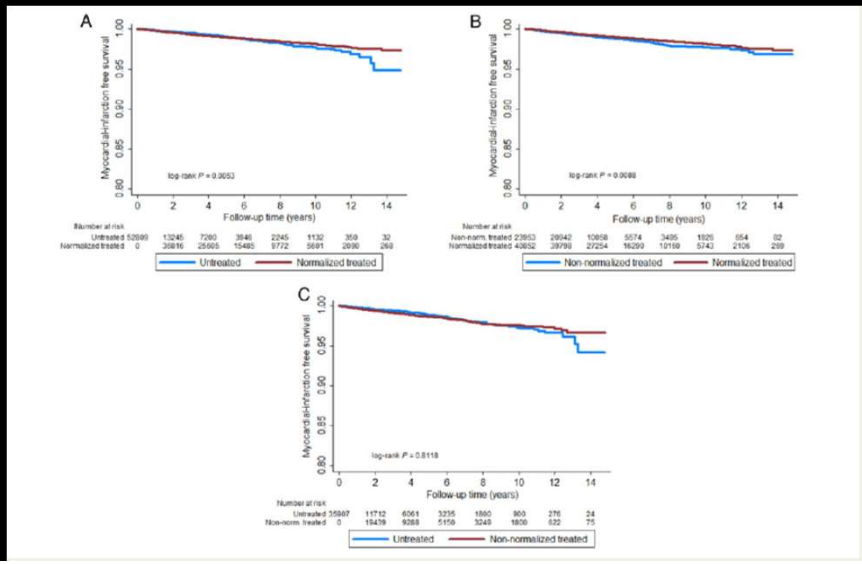
Model	All-cause mortality			Myocardial infarction			Stroke		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Comparing normalized treated vs. untreated (ref = untreated)									
Univariate N = 43 931 vs. 13 378	0.40	0.39–0.43	<0.001	0.70	0.59–0.83	<0.001	0.57	0.40–0.82	0.002
Propensity matched (stabilized inverse probability of treatment weights) N = 40 852 vs. 11 957	0.44	0.42–0.46	<0.001	0.76	0.63–0.93	0.005	0.64	0.43–0.96	0.031
Comparing normalized treated vs. non-normalized treated (ref = non-normalized treated)									
Univariate N = 43 931 vs. 25 701	0.49	0.47–0.51	<0.001	0.74	0.64–0.85	<0.001	0.64	0.48–0.87	0.004
Propensity matched (stabilized inverse probability of treatment weights) N = 40 852 vs. 23 953	0.53	0.50–0.55	<0.001	0.82	0.71–0.95	0.008	0.70	0.51–0.96	0.028
Comparing non-normalized treated vs. untreated (ref = untreated)									
Univariate N = 25 701 vs. 13 378	0.83	0.79–0.87	<0.001	0.95	0.79–1.15	0.599	0.90	0.61–1.34	0.610
Propensity matched (stabilized inverse probability of treatment weights) N = 23 953 vs. 11 957	0.84	0.80–0.89	<0.001	0.98	0.80–1.19	0.811	0.94	0.61–1.44	0.675

Sharma R et al. Eur Heart J, published online August 06, 2015; doi: 10.1093/eurheartj/ehv346

ALL-CAUSE MORTALITY



MYOCARDIAL INFARCTION



ORIGINAL RESEARCH

Normalization of Testosterone Levels After Testosterone Replacement Therapy Is Associated With Decreased Incidence of Atrial Fibrillation

Rishi Sharma, MD, MHSA; Olurinde A. Oni, MBBS, MPH; Kamal Gupta, MD; Mukut Sharma, PhD; Ram Sharma, PhD; Vikas Singh, MD, MHSA; Deepak Parashara, MD; Surineni Kamalakar, MBBS, MPH; Buddhadeb Dawn, MD; Guoqing Chen, MD, PhD, MPH; John A. Ambrose, MD; Rajat S. Barua, MD, PhD

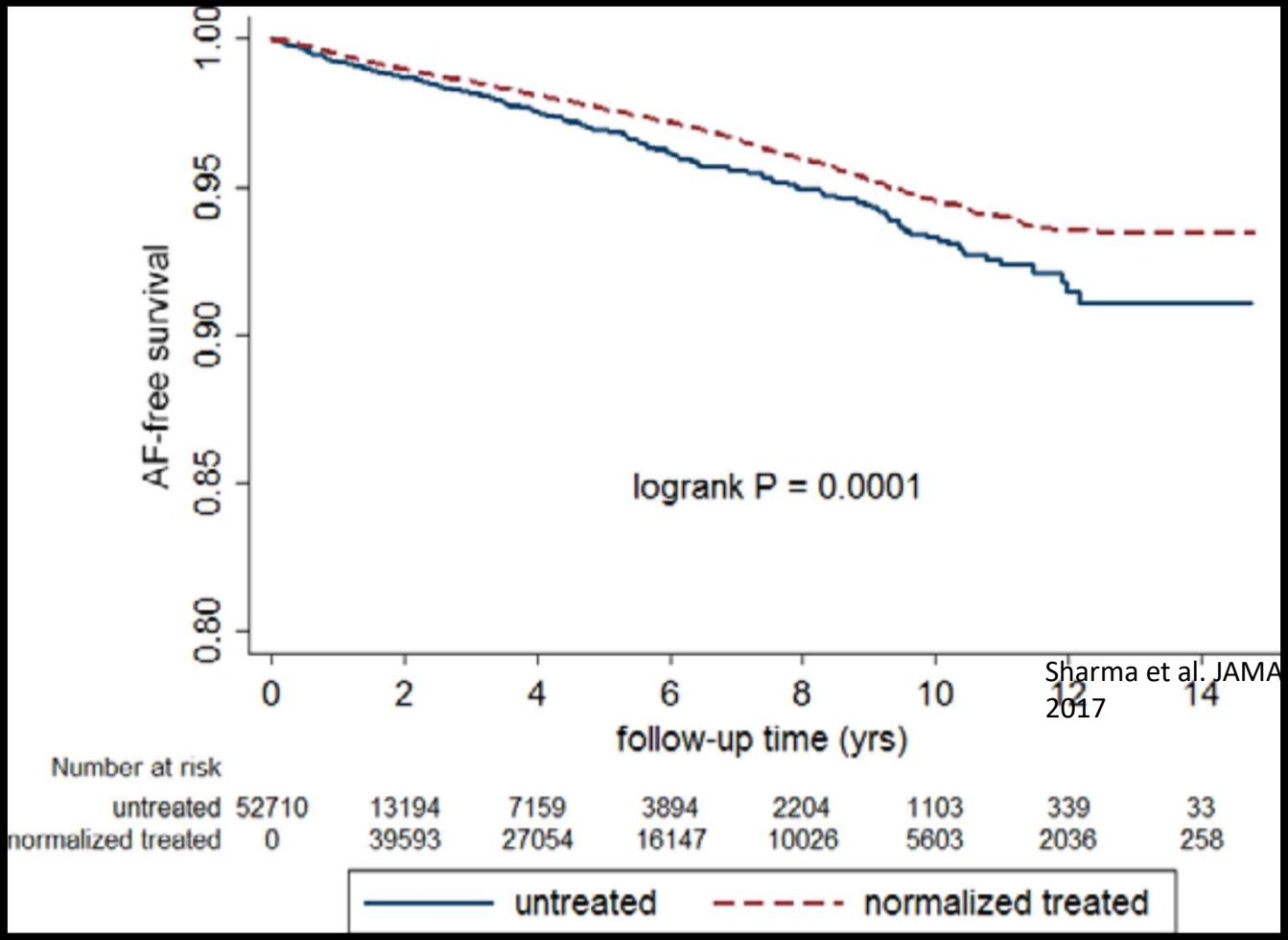
Background—Atrial fibrillation (AF) is the most common cardiac dysrhythmia associated with significant morbidity and mortality. Several small studies have reported that low serum total testosterone (TT) levels were associated with a higher incidence of AF. In contrast, it is also reported that anabolic steroid use is associated with an increase in the risk of AF. To date, no study has explored the effect of testosterone normalization on new incidence of AF after testosterone replacement therapy (TRT) in patients with low testosterone.

Methods and Results—Using data from the Veterans Administrations Corporate Data Warehouse, we identified a national cohort of 76 639 veterans with low TT levels and divided them into 3 groups. Group 1 had TRT resulting in normalization of TT levels (normalized TRT), group 2 had TRT without normalization of TT levels (nonnormalized TRT), and group 3 did not receive TRT (no TRT). Propensity score–weighted stabilized inverse probability of treatment weighting Cox proportional hazard methods were used for analysis of the data from these groups to determine the association between post-TRT levels of TT and the incidence of AF. Group 1 (40 856 patients, median age 66 years) had significantly lower risk of AF than group 2 (23 939 patients, median age 65 years; hazard ratio 0.90, 95% CI 0.81–0.99, P=0.0255) and group 3 (11 853 patients, median age 67 years; hazard ratio 0.79, 95% CI 0.70–0.89, P=0.0001). There was no statistical difference between groups 2 and 3 (hazard ratio 0.89, 95% CI 0.78– 1.0009, P=0.0675) in incidence of AF.

Conclusions—These novel results suggest that normalization of TT levels after TRT is associated with a significant decrease in the incidence of AF. **(*J Am Heart Assoc*. 2017;6:e004880. DOI: 10.1161/JAHA.116.004880.)**

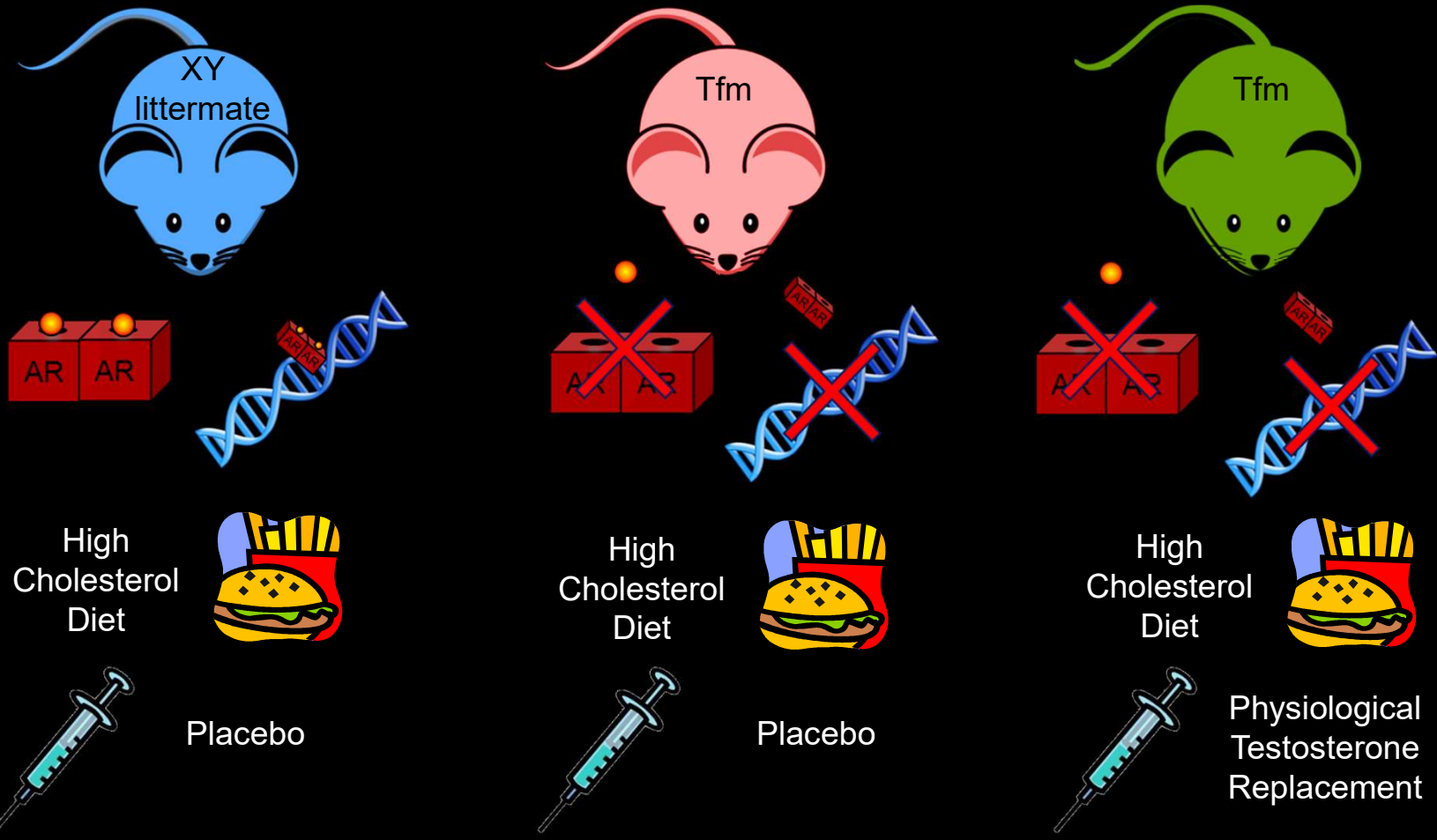
Key Words: atrial fibrillation • testosterone • testosterone replacement therapy

Normalisation of Testosterone is Associated with a Significantly Reduced Risk of Atrial Fibrillation

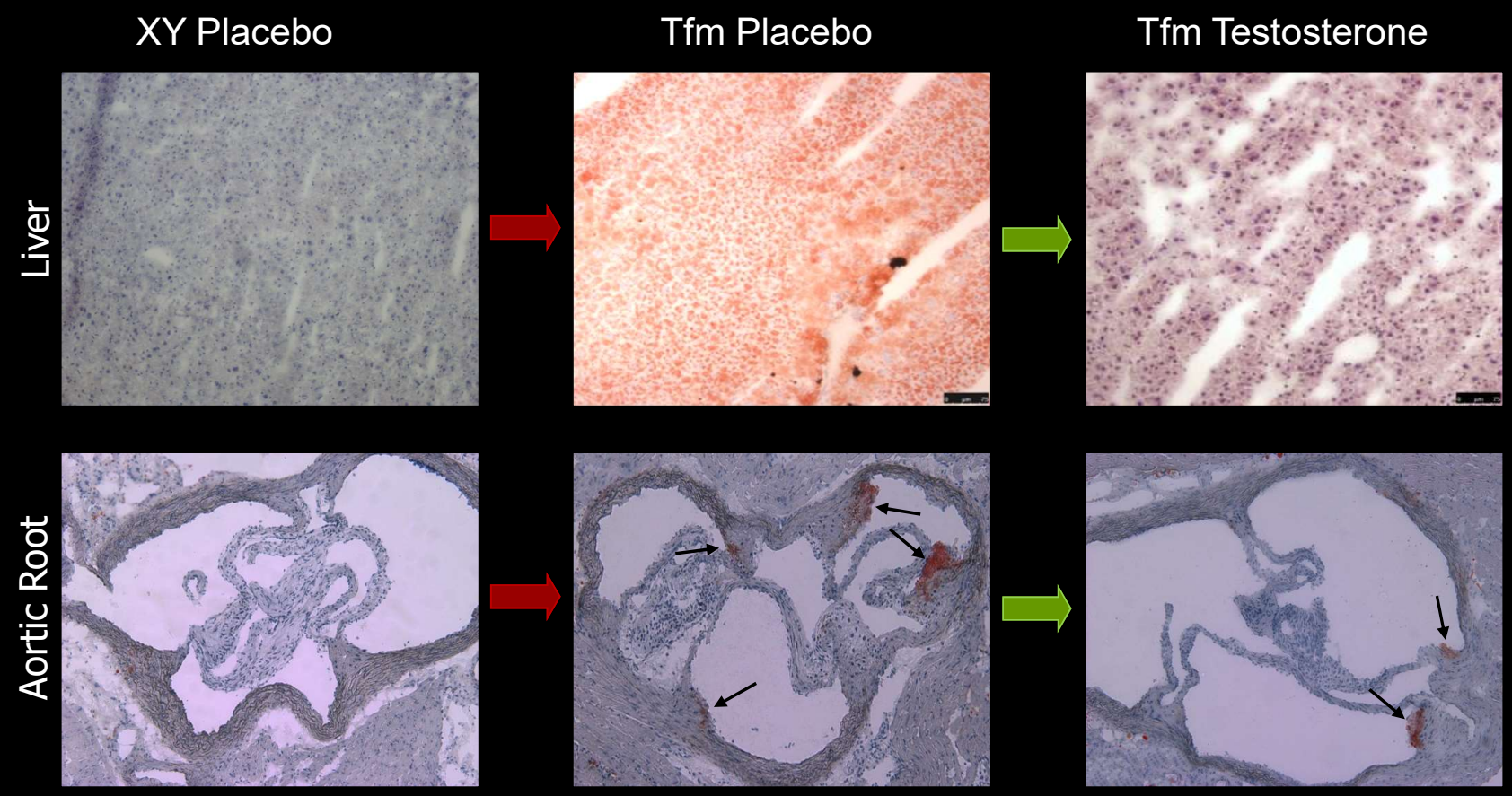


Sharma et al. JAMA 2017

Testicular Feminized (Tfm) Mouse

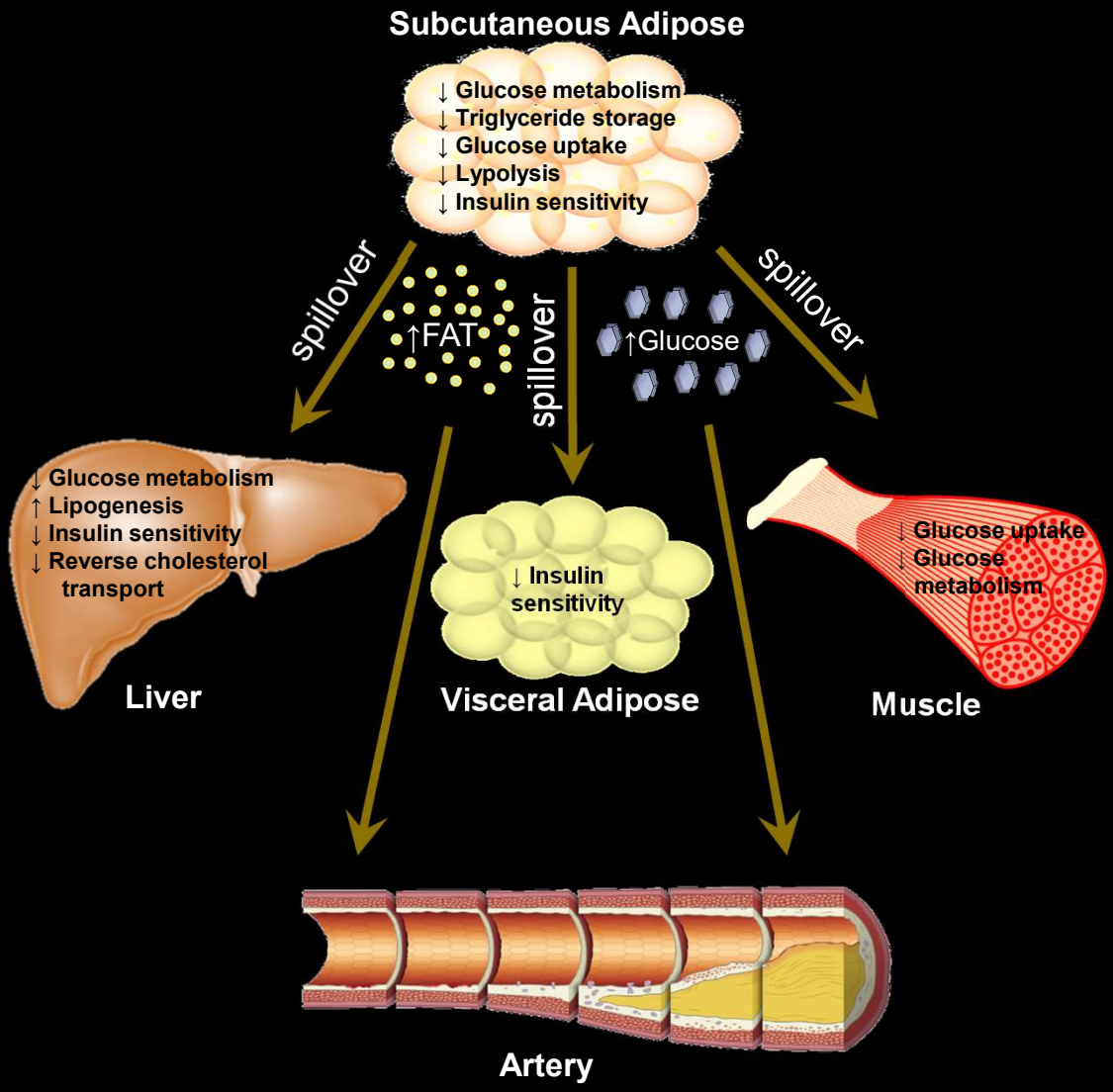


Lipid Deposition

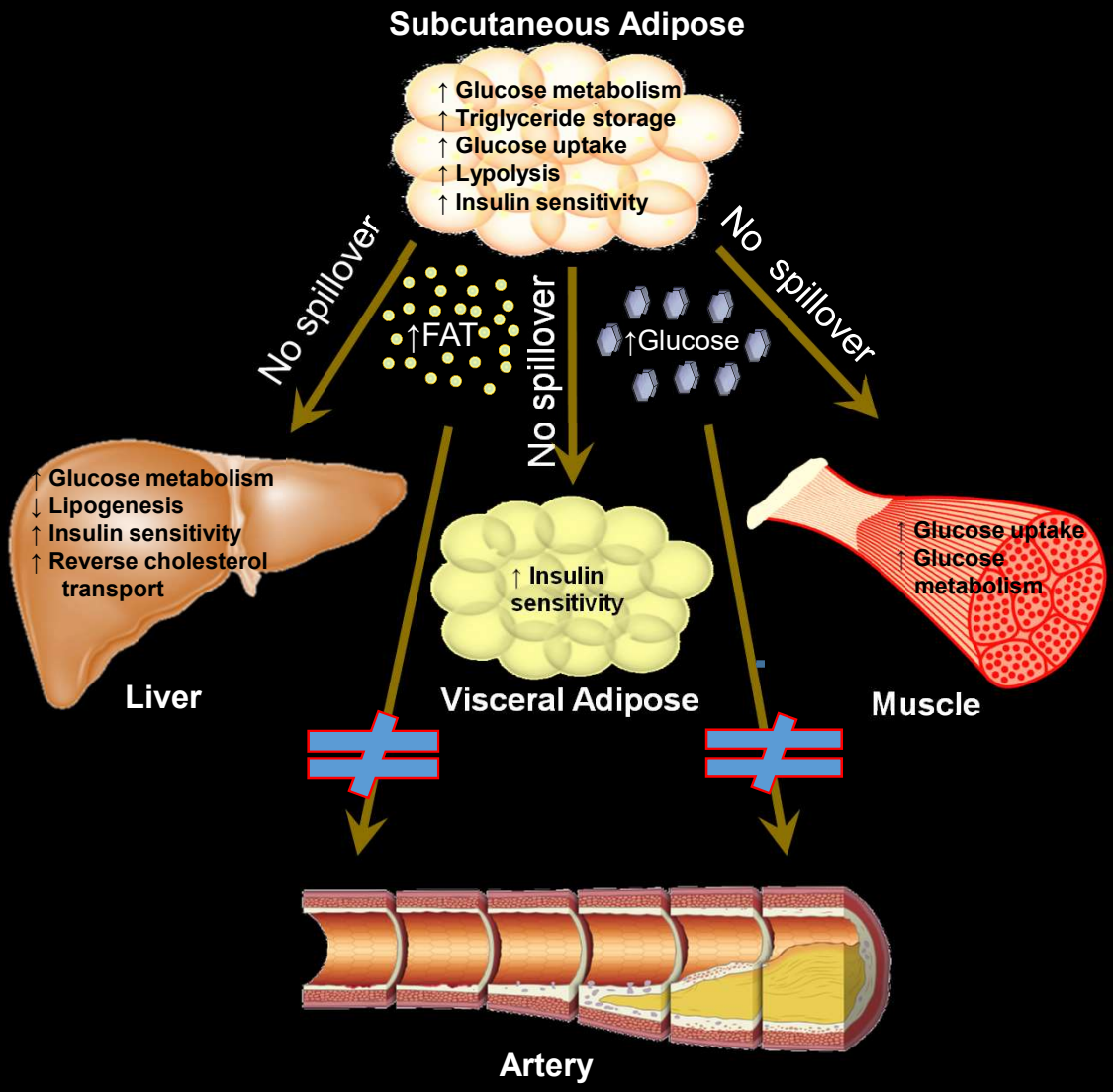


TESTOSTERONE DEFICIENCY

SPILLOVER HYPOTHESIS



TESTOSTERONE BUFFER and SPILLOVER HYPOTHESIS



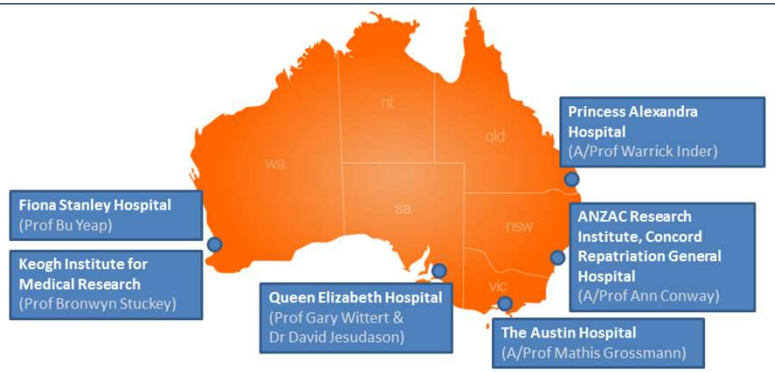
ANZ Clinical Trial Registry number: ACTRN12612000287831

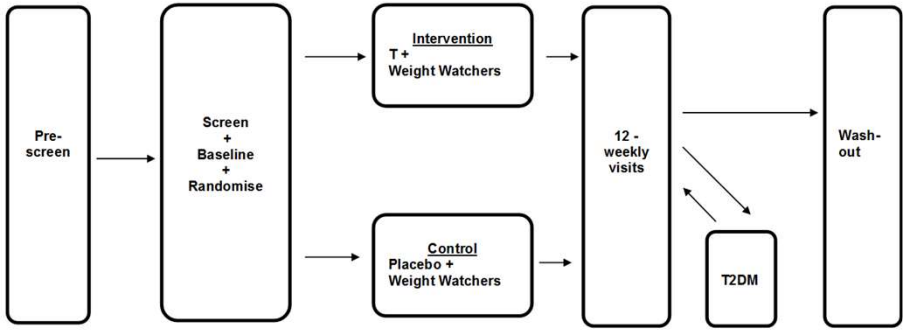
Testosterone for T2D prevention in men: 2-year multicentre, randomised, double-blind, placebo-controlled trial

Injectable testosterone undecanoate (Reandron, Bayer AG) (1000mg/4ml) or vehicle at baseline, 6 weeks, and then 3 monthly thereafter for 2-4 years

Primary endpoints
(1) proportion with 2-hour OGTT ≥ 11.1 mmol/L
(2) difference of at least 0.6mmol/L in the mean 2-hour OGTT glucose
Power: 80% and 90% respectively, for sample size 1000 with sig level 2.5%.

Men aged 50-74 years
Waist circumference ≥ 95cm
T ≤ 14 nmol/L
Impaired glucose tolerance or newly diagnosed diabetes - OGTT
No T treatment in last 12 months
No active heart disease or liver disease
No history of cancer (other than non-melanoma skin)





Sub-studies
T4Bone – Changes in bone microarchitecture
T4MB – Mood and behaviour
Telomere length
T4DM Run-on – effects of extended treatment for up to 4 years
T4DM Run-off – rate of recovery of the hypothalamo-pituitary testicular axis

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ABCD NATIONAL AUDIT OF TESTOSTERONE THERAPY IN HYPOGONADAL MEN WITH TYPE 2 DIABETES MELLITUS

Hypogonadism and Type 2 Diabetes
Summary

- Hypogonadism in Type 2 Diabetes is common
- Sexual dysfunction is common in men with Type 2 diabetes affecting QOL
- Sexual function can be improved with TRT plus or minus other treatment modalities e.g. PDE5 inhibitors, psychology
- Low T is a major risk factor for mortality and survival
- Low T is associated with adverse effects on CV risk factors
- Evidence suggests that TRT improves Insulin resistance, obesity and dyslipidaemia and may include glycaemic control
- Whether or normalisation of testosterone levels reduces MACE will require a large RCT – TRAVERSE STUDY with 6000 subjects
- There is accumulating scientific rationale for supporting the clinical benefits.