Debate

This house believes that every obese male patient with Type 2 Diabetes should be screened for Hypogonadism

For the Motion

Hugh Jones

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

ISA, ISSAM and EAU Guidelines for Late-onset Hypogonadism (2006)

'A clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels.

It may result in significant detriment in the quality of life and adversely affect the function of multiple organ systems.'

Nieschlag et al. Int J Androl; 28: 125

Key Symptoms / Signs of Hypogonadism (LOH)

- Low Libido
- Erectile Dysfunction
- Loss of morning/nocturnal erections
- Decreased muscle mass and strength
- Increased body fat
- Decreased Vitality
- Depressed Mood
- Decreased BMD / Osteoporosis

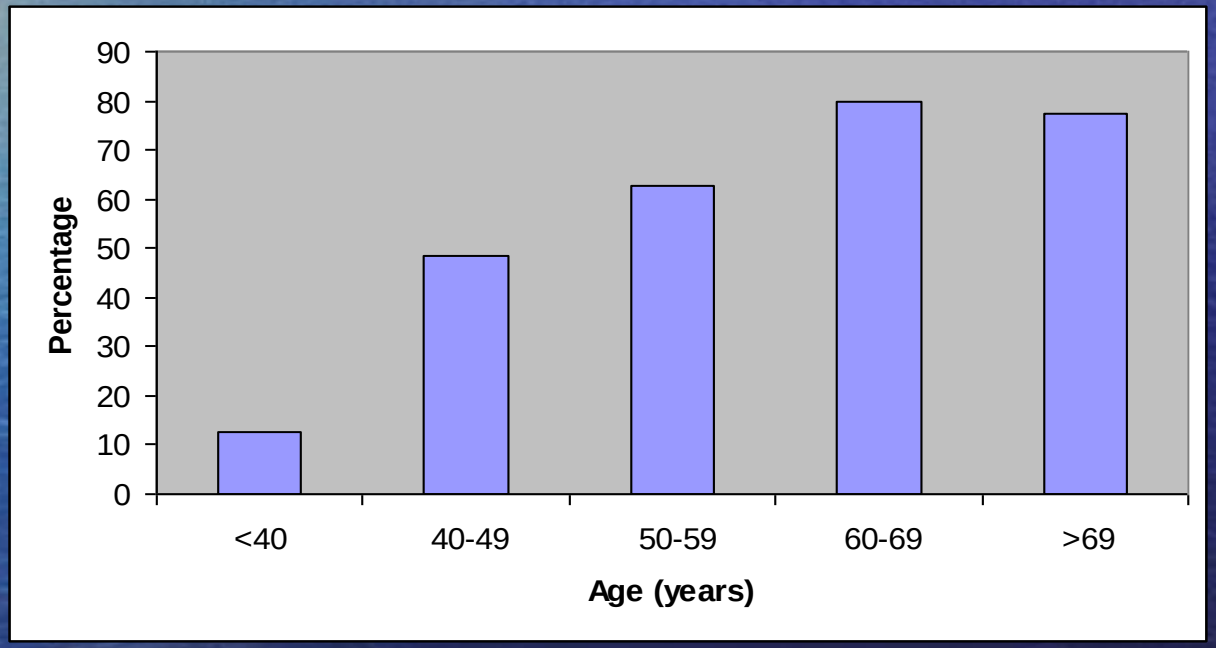
Symptoms & Signs Suggestive of Androgen Deficiency

(Endocrine Society Guidelines 2006)

- ↓ Libido and activity
- ↓ Erectile Function (ED)
- ↓ Spontaneous erections
- ↓ Muscle bulk / strength
- ↓ Height, BMD
- Hot flushes / sweats
- Loss body hair, ↓ shaving
- Gynaecomastia
- Inability to father children
- ↓ energy, motivation, aggression, initiative, self-confidence
- ↓ Concentration / memory
- Feeling sad or blue, depressed mood, dysthymia
- Sleep disturbance
- Mild anaemia
- – Body fat, BMI
- ↓ Physical or work performance

Bhasin S. Et al J. Clin Endocrinol Metab 2006;91:1995

Prevalence of Erectile Dysfunction in Men with Type 2 Diabetes



TYPE 2 DIABETES

National clinical guideline for management in primary and secondary care (update)

RECOMMENDATIONS

R123 Review the issue of erectile dysfunction with men annually.

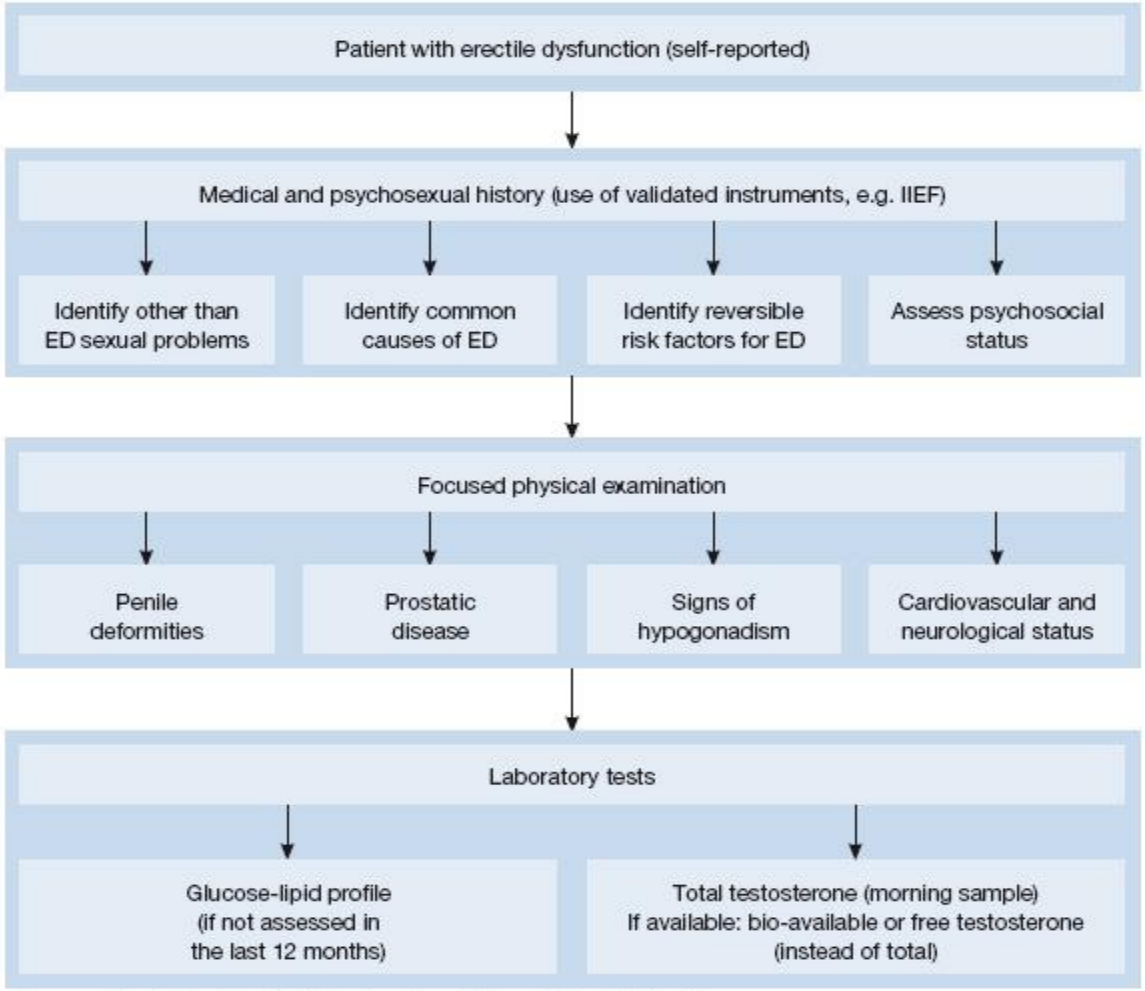
R124 Provide assessment and education for men with erectile dysfunction to address contributory factors and treatment options.

R125 Offer a phosphodiesterase-5 inhibitor (choosing the drug with the lowest acquisition cost), in the absence of contraindications, if erectile dysfunction is a problem.

R126 Following discussion, refer to a service offering other medical, surgical, or psychological management of erectile dysfunction if phosphodiesterase-5 inhibitors have been unsuccessful.

European Association of Urology Guidelines on Erectile Dysfunction

Figure 1: Minimal diagnostic evaluation (basic work-up) in patients with ED



ED = erectile dysfunction; IIEF = International Index of Erectile Function.

Wespes E. et al. Eur Urol 2006;49:806-15

European Journal of Endocrinology (2008) **159** 507–514 ISSN 0804-4643

CONSENSUS STATEMENT

Investigation, treatment and monitoring of late-onset hypogonadism in males

ISA, ISSAM, EAU, EAA and ASA recommendations

C Wang, E Nieschlag[1], R Swerdloff, H M Behre[2], W J Hellstrom[3], L J Gooren[4], J M Kaufman[5], J-J Legros[6], B Lunenfeld[7], A Morales[8], J E Morley[9], C Schulman[10], I M Thompson[11], W Weidner[12] and F C W Wu[13]

Division of Endocrinology, Department of Medicine, Harbor-UCLA Medical Center and Los Angeles BioMedical Research Institute, General Clinical Research Center, 1000 W. Carson Street, Torrance, California 90509, USA, [1]Centre for Reproductive Medicine and Andrology, University of Muenster, Muenster, Germany, [2]Center for Reproductive Medicine and Andrology, University Hospital Halle, Martin-Luther-University Halle-Wittenberg, Halle, Germany, [3]Department of Urology, Tulane University, New Orleans, Los Angeles, USA, [4]Department of Endocrinology, VU University Medical Center, Amsterdam, The Netherlands, [5]Department of Endocrinology, Academish Ziekenhuis, Gent, Belgium, [6]Centre Hospitalier Universitaire, Sart-Tilman, Liège, Belgium, [7]Faculty Life Science, Bar-Ilan University, Ramat-Gan, Israel, [8]Centre for Applied Urological Research, Queen's University, Kingston, Canada, [9]Division of Geriatric Medicine, St Louis VA Medical Center, St Louis University, and GRECC, St Louis, Missouri, USA, [10]Department of Urology, Erasme Hospital, University Clinics Brussels, Brussels, Belgium, [11]Department of Urology, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA, [12]Department of Urology and Pediatric Urology, University Hospitals, Justus-Liebig-University, Giessen, Germany and [13]Department of Endocrinology, University of Manchester, Manchester Royal Infirmary, Manchester, UK

(Correspondence should be addressed to C Wang; Email: wang@labiomed.org)

European Association of Urology

Guidelines

Investigation, Treatment, and Monitoring of Late-Onset Hypogonadism in Males: ISA, ISSAM, EAU, EAA, and ASA Recommendations

Christina Wang[a,*], *Eberhard Nieschlag*[b], *Ronald Swerdloff*[a], *Hermann M. Behre*[c], *Wayne J. Hellstrom*[d], *Louis J. Gooren*[e], *Jean M. Kaufman*[f], *Jean-Jacques Legros*[g], *Bruno Lunenfeld*[h], *Alvaro Morales*[i], *John E. Morley*[j], *Claude Schulman*[k], *Ian M. Thompson*[l], *Wolfgang Weidner*[m], *Frederick C.W. Wu*[n]

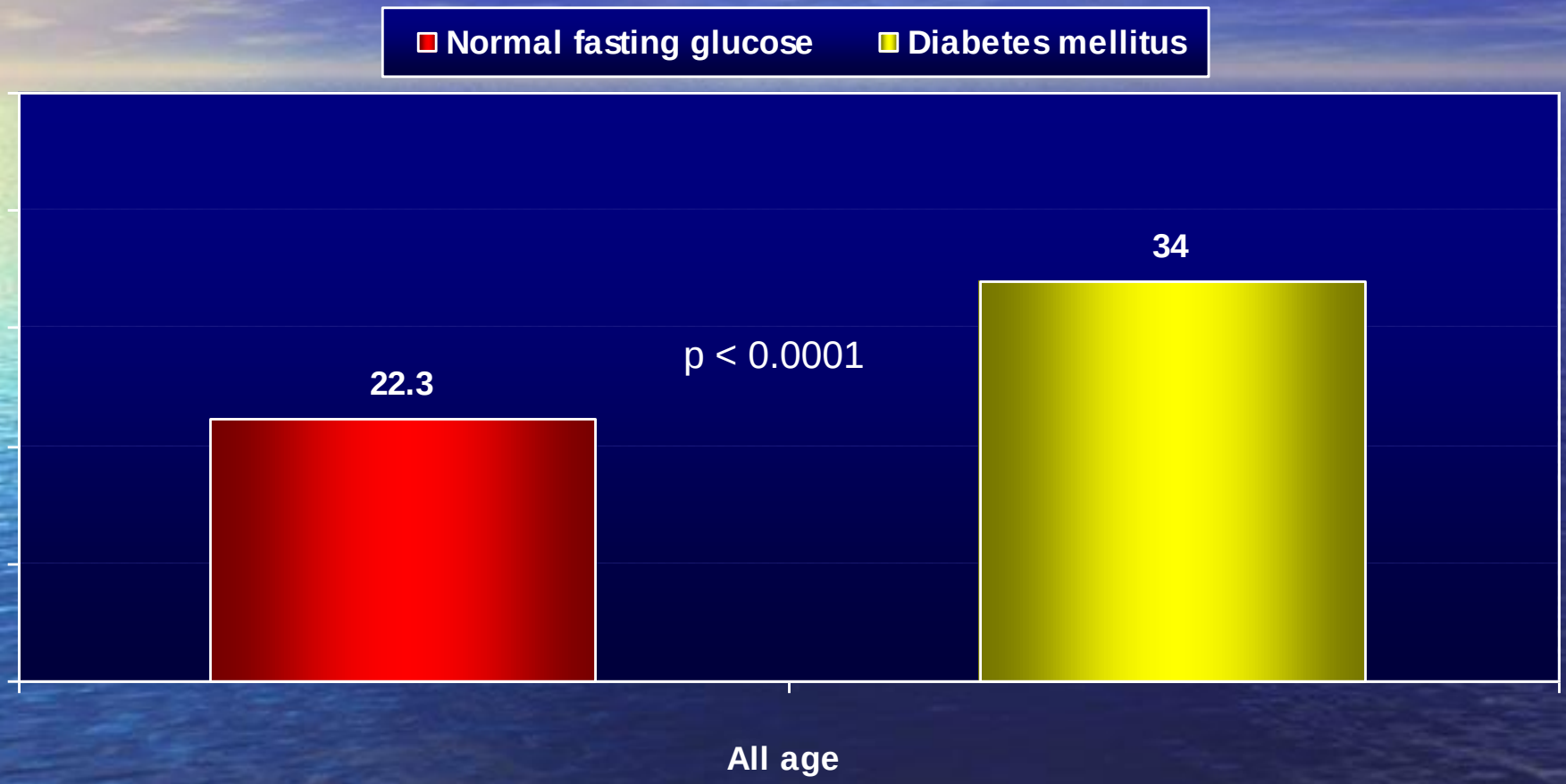
10. Recommendation 8: Testosterone and obesity, metabolic syndrome, and type 2 diabetes

The metabolic syndrome and type 2 diabetes mellitus are associated with low plasma testosterone [25,55,57–62]. Serum testosterone should be measured in men with type 2 diabetes mellitus with symptoms suggestive of testosterone deficiency (level 2b, grade A).

Testosterone and Erectile Function


PLEASE DO NOT TOUCH OR
CLIMB ON THIS SCULPTURE

Prevalence of Hypogonadism (T < 12 nmol/L) in 1,027 Diabetic and Non-Diabetic Patients with Erectile Dysfunction



Corona G et al. Eur Urol 46(2): 222-228 (2004)

Risk Factors Associated with Erectile Dysfunction in men with Type 2 Diabetes

	Prevalence of ED in cases	**Prevalence of ED in controls**	χ^2	**p**
Hypertension	91 (71%)	38 (55%)	4.74	**0.03**
BMI >30	94 (69%)	35 (57%)	2.35	0.13
Waist circumference >102cms	110 (69%)	19 (50%)	4.99	**0.03**
Smokers	87 (70%)	42 (57%)	3.67	0.06
Alcohol intake	106 (66%)	23 (62%)	0.18	0.67

Kapoor et al, Int J Androl 2007 ; 30:500-7

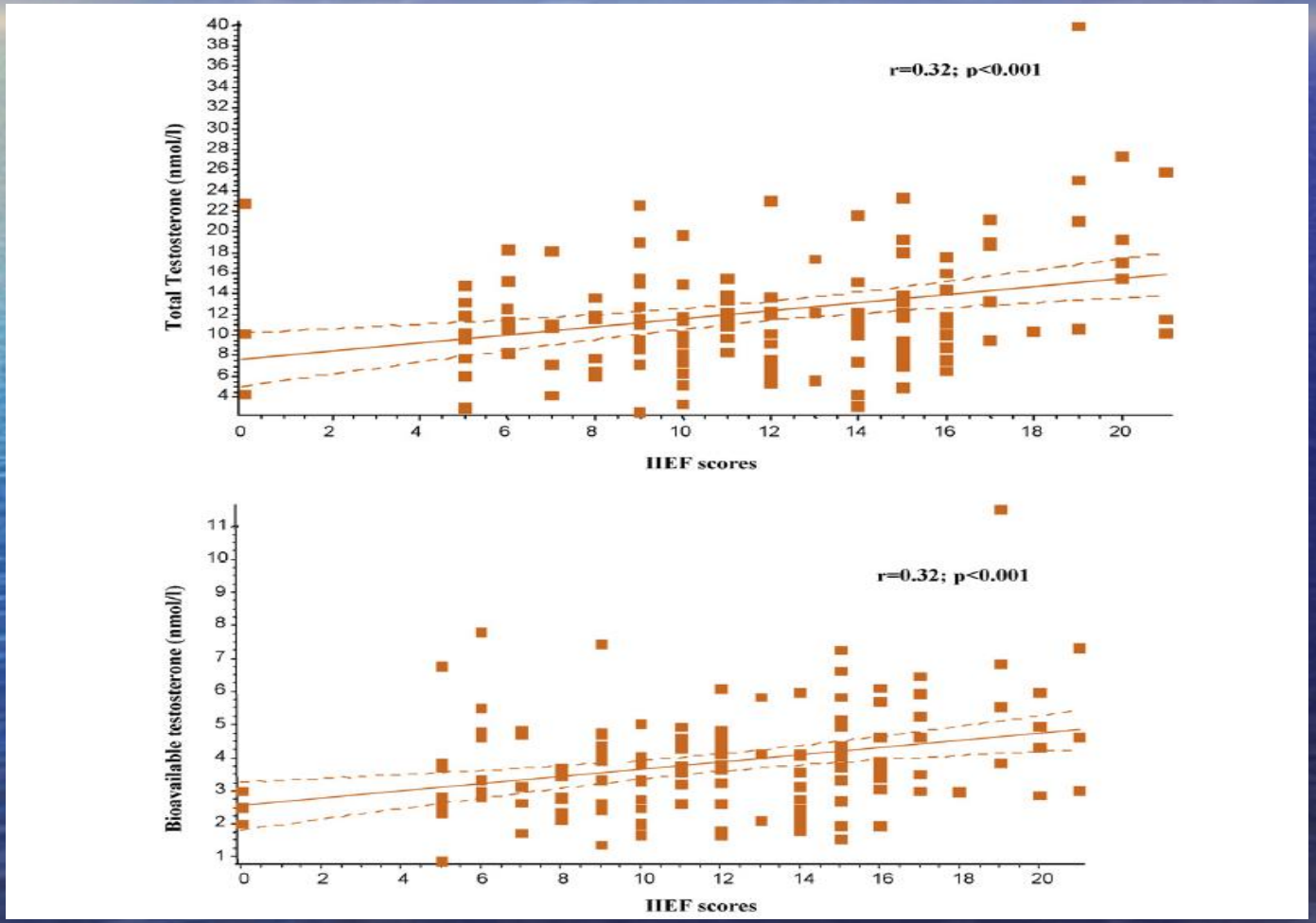
Correlation between Bioavailable Testosterone and Waist Circumference

Bioavailable testosterone (nmol/l)

r= -0.21 p<0.001

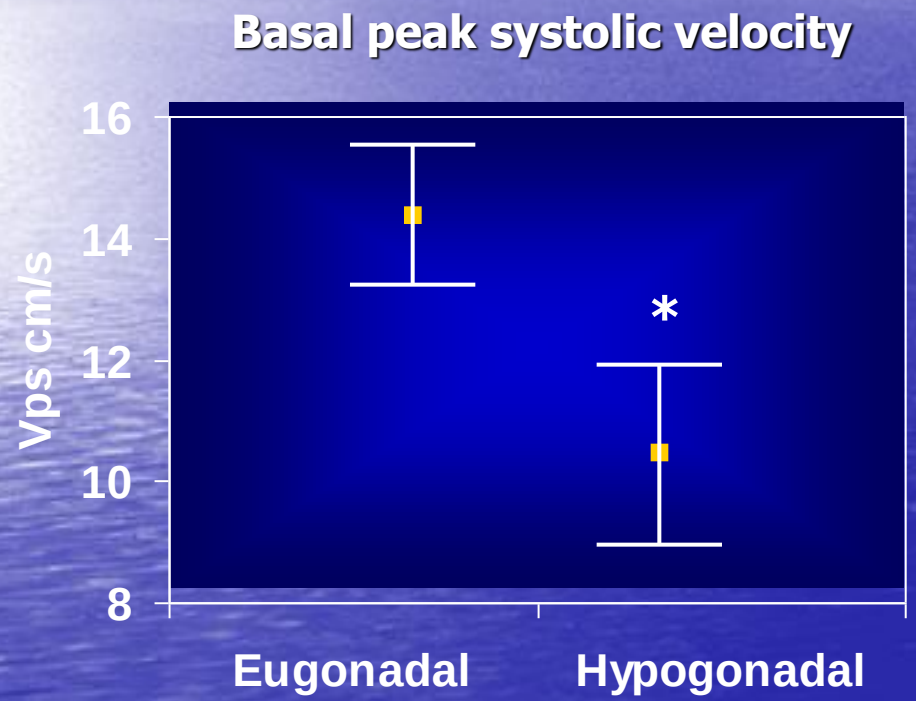
Kapoor D et al. Diabetes Care 30: 911–917 (2007)

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

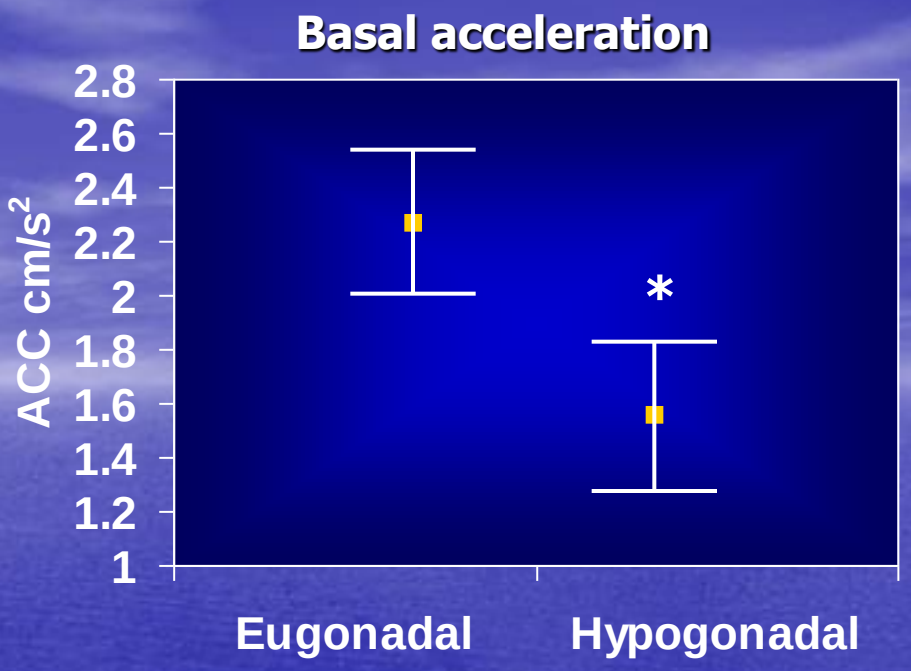


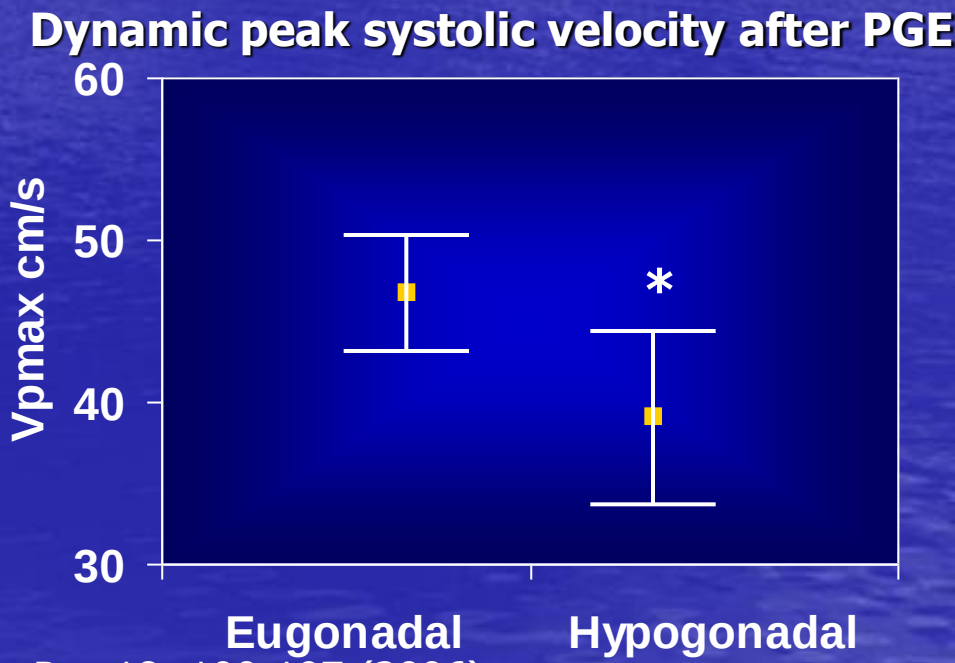
Kapoor et al, Int J Androl 2007 ; 30:500-7

Penile Doppler Ultrasound in Eugonadal and Hypogonadal Type 2 Diabetic Men



* p< 0.0001





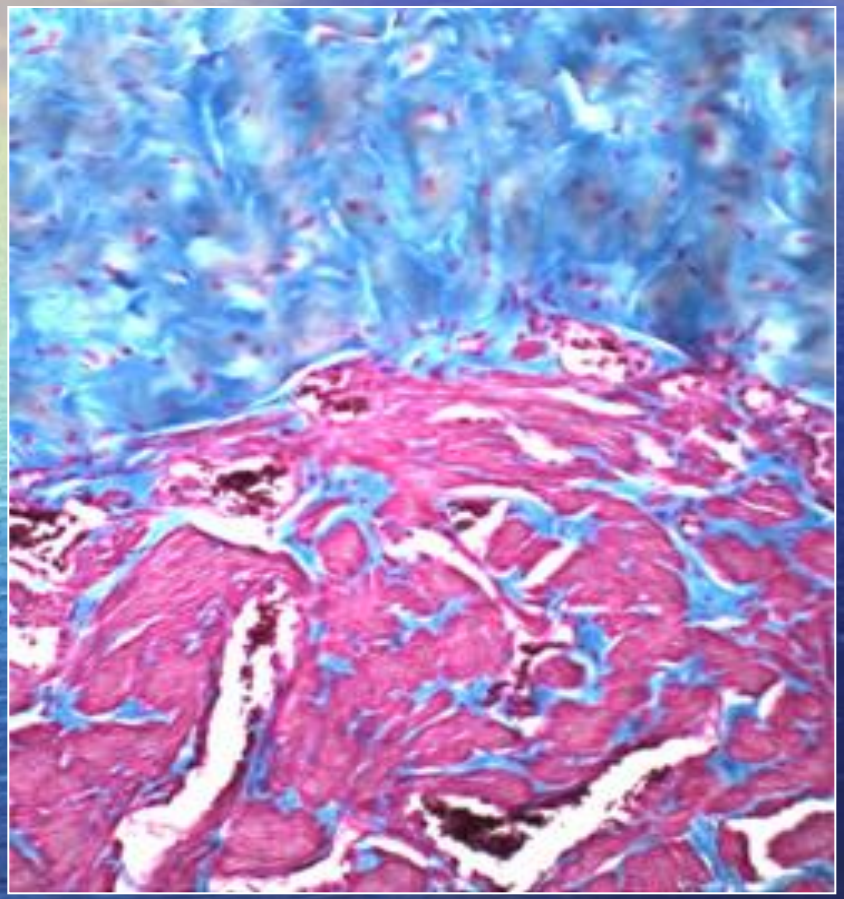
Corona G et al. Int J Impot Res 18: 190-197 (2006)

Animal Experiments

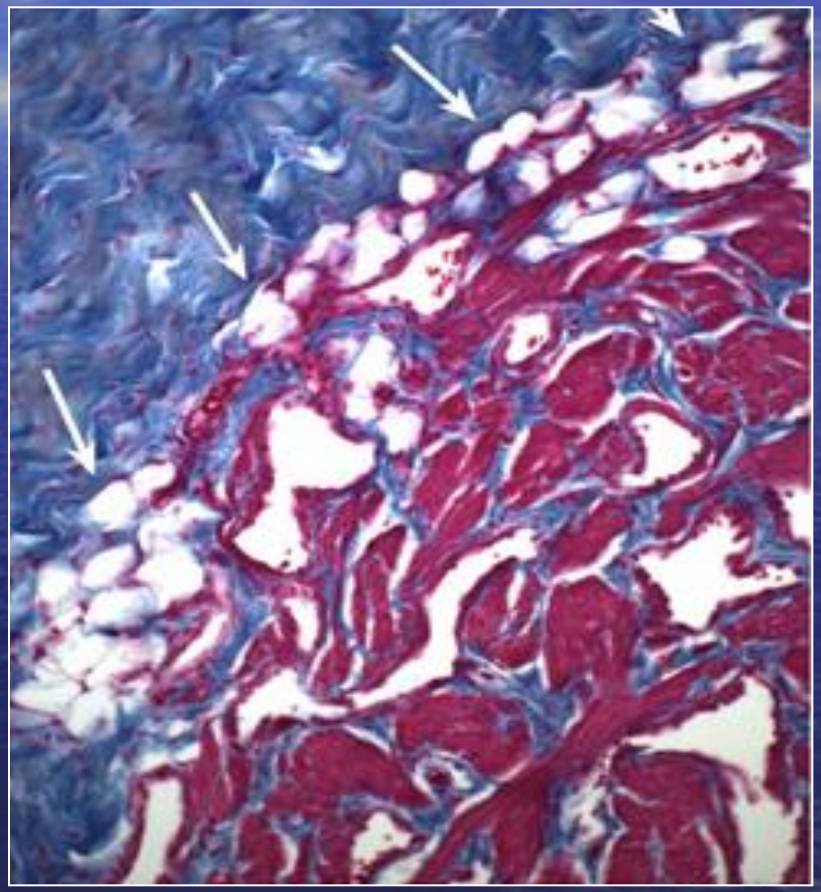
Testosterone Deficiency Results in Structural Changes in Erectile Tissue Components:

- **nerve fibers**
- **smooth muscle content**
- **connective tissue**
- **adipogenesis**

Testosterone Deprivation Promotes Adipocyte Accumulation in the Penile Corpus Cavernosum



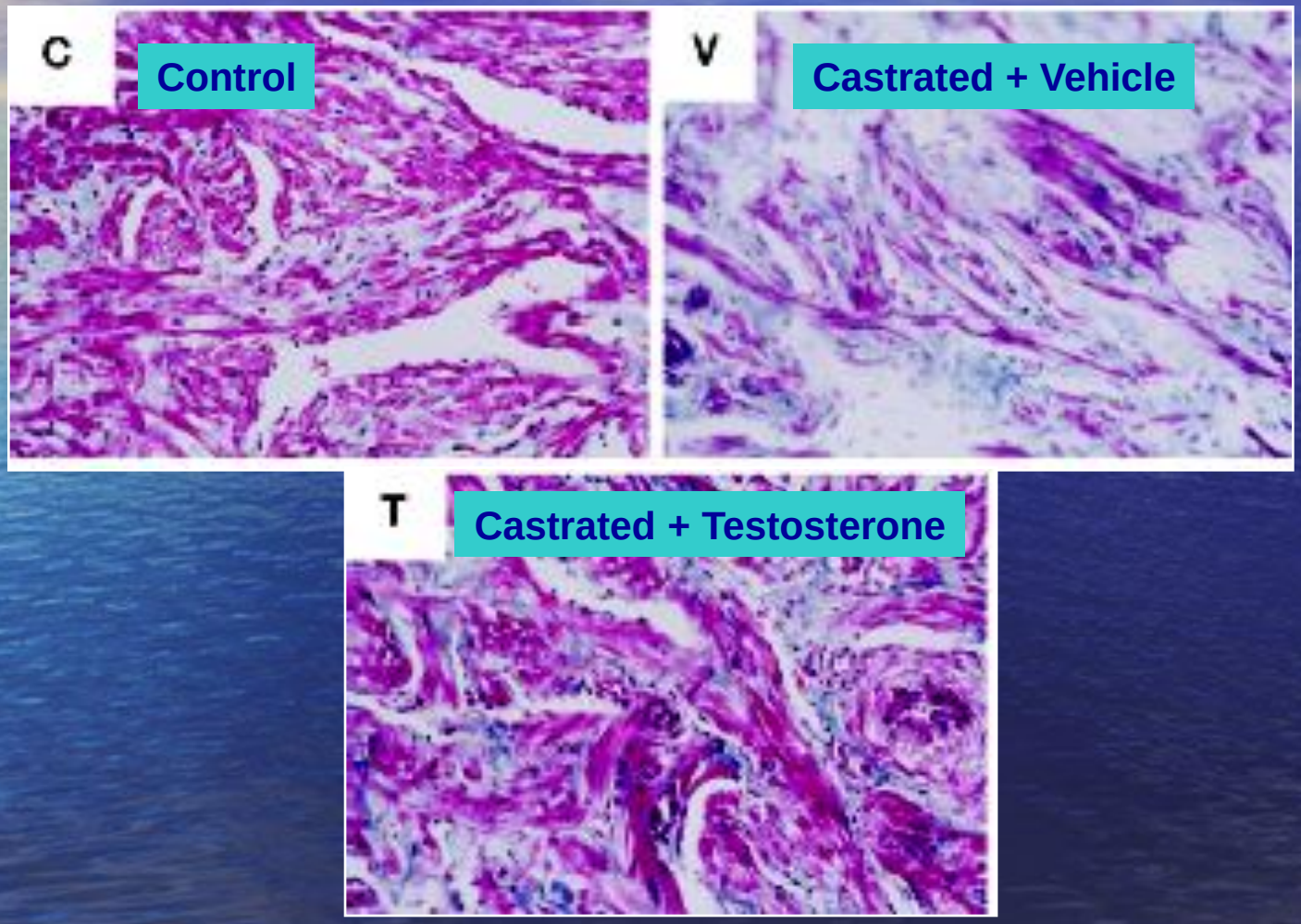
Control



Castrated

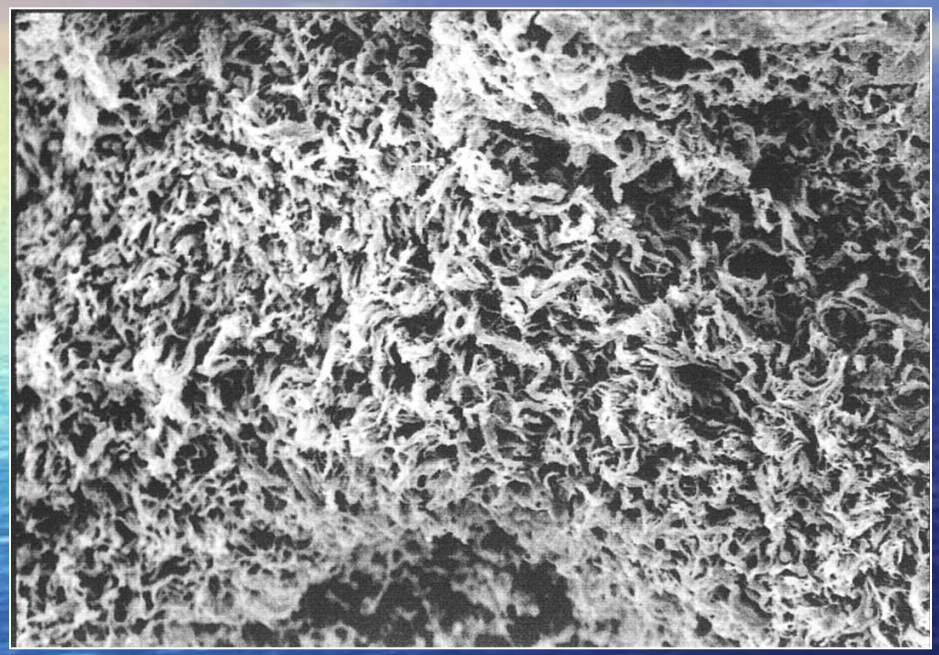
Traish A et al. J Androl 26(2): 88-94 (2005)

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



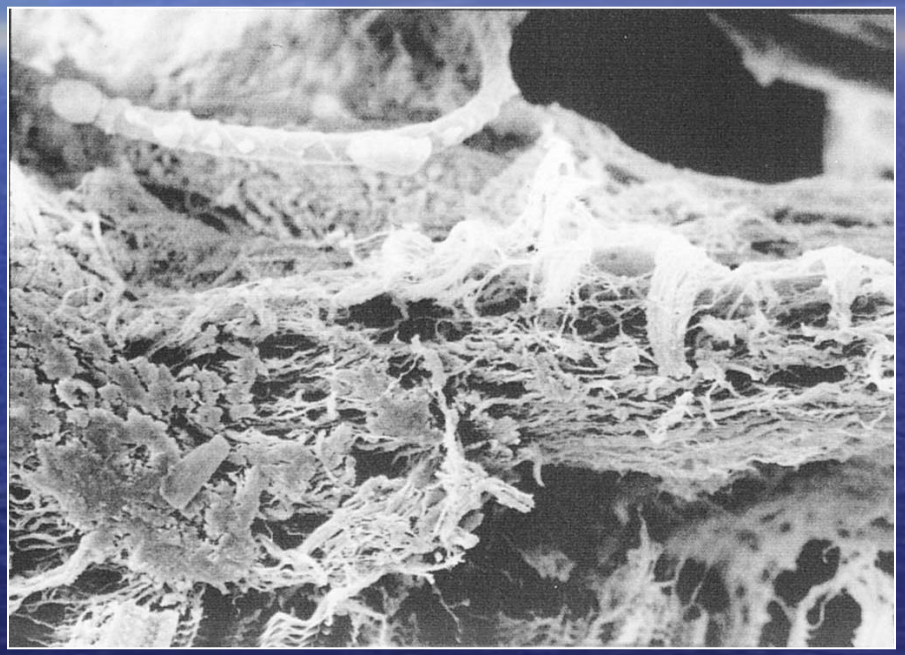
Traish A et al. Endocrinol 140(4): 1861-1868 (1999)

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



Group A:

Control rich, regularly arranged elastic fibers

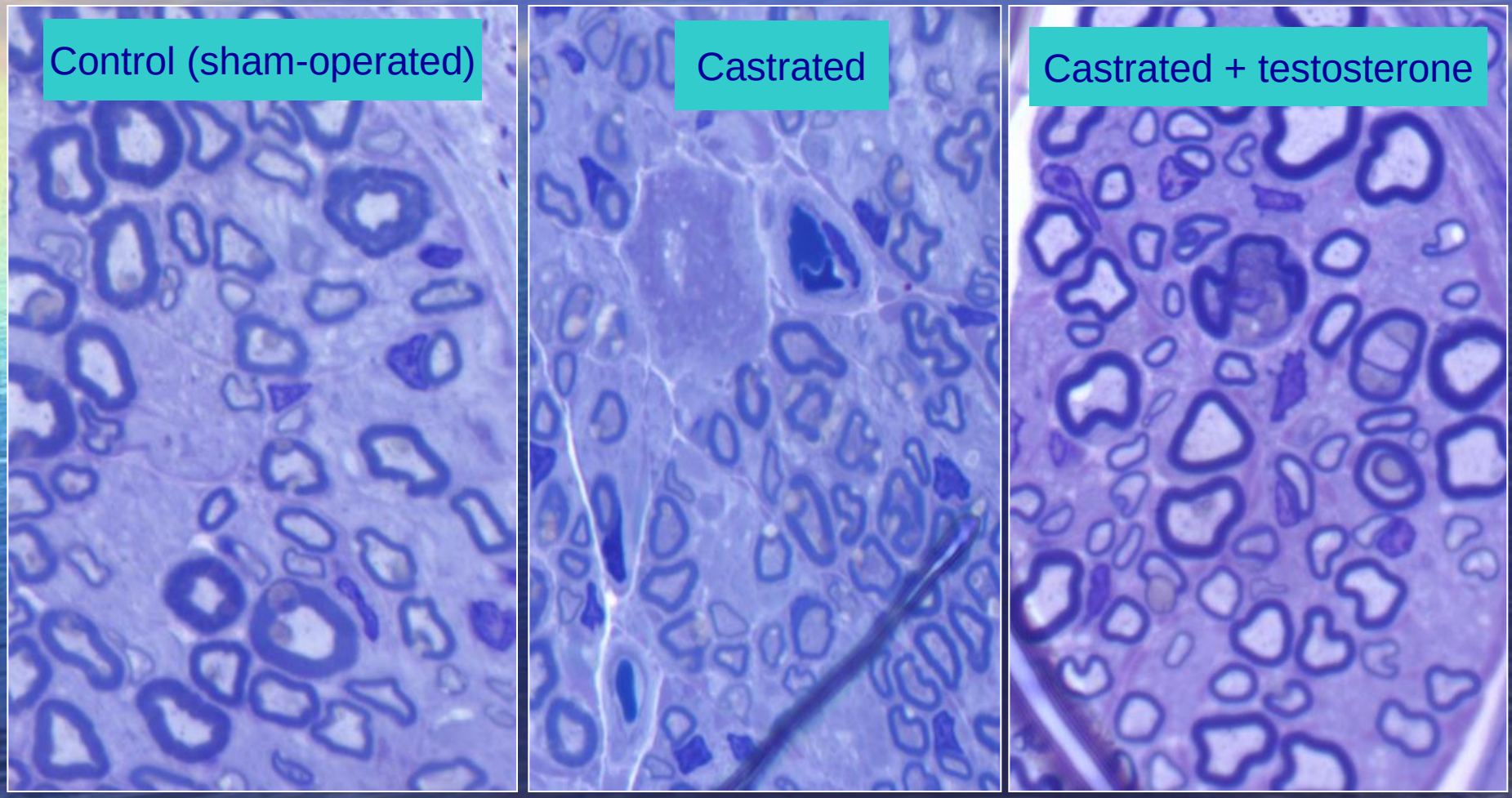


Group B:

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



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

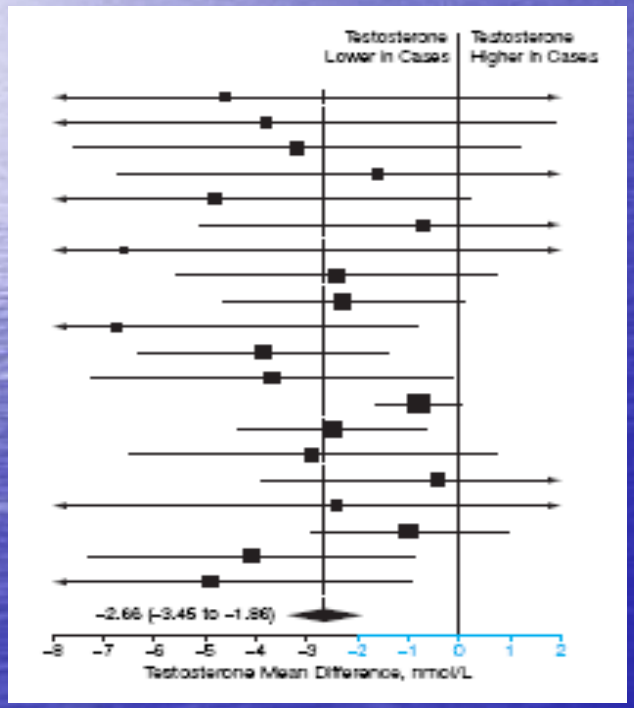
Different Testosterone Levels in Diabetic Responders and Non-Responders to PDE5 Inh.

	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)	

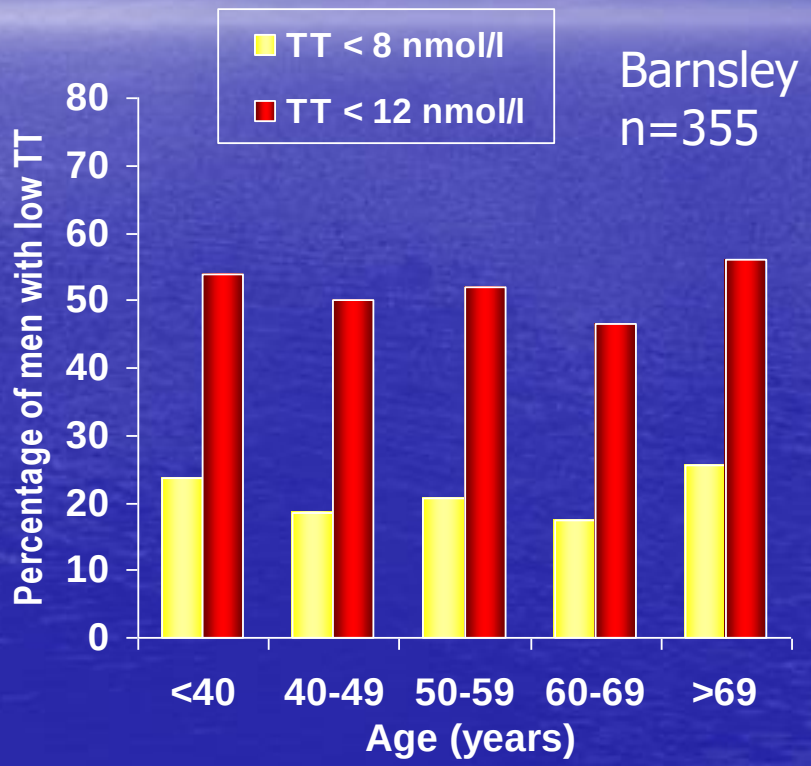
Kalinchenko S et al. Aging Male 6: 94-99 (2003)

Total Testosterone in men with Type 2 Diabetes

Meta-analysis
20 studies 1982-2005



Ding L et al. JAMA 295:1288-1299



Barnsley Study
n=355

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)

Bioavailable and Free Testosterone. Biologically active fractions in men with Type 2 Diabetes

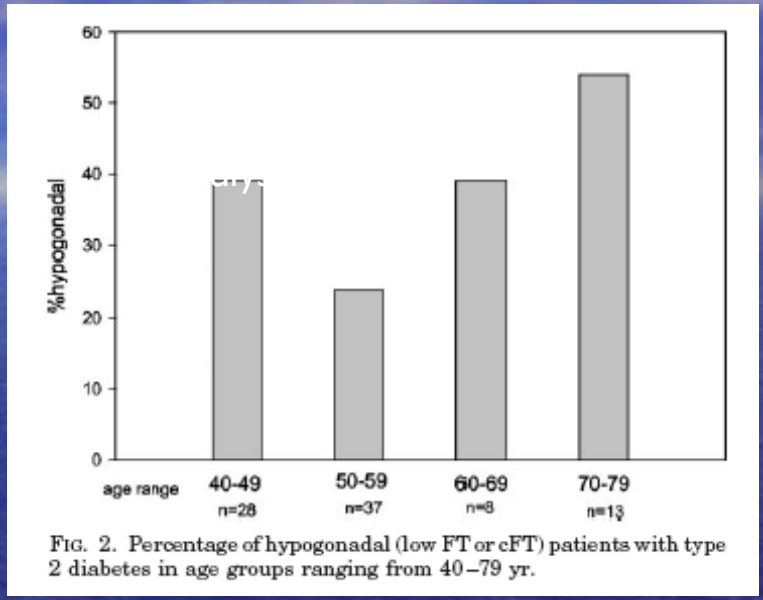


FIG. 2. Percentage of hypogonadal (low FT or cFT) patients with type 2 diabetes in age groups ranging from 40–79 yr.

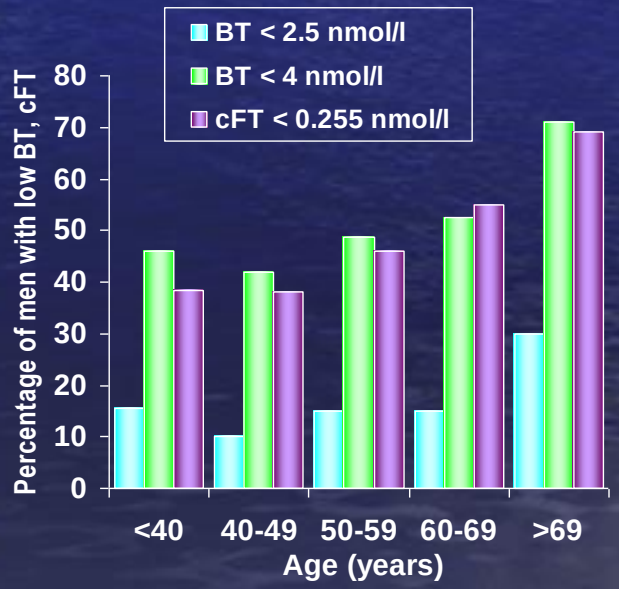
Bioavailable Testosterone

20-40% bound to albumin

~0.5-2% free

60-80% bound to SHBG

Biologically Inactive?



Dhindsa S et al JCEM 89:5462-8 (2004)
Kapoor D et al. Diabetes Care 30: 911–917 (2007)

Causes of Hypogonadism

Primary Hypogonadism 26%

Secondary Hypogonadism 10%

'Normogonadotrophic' Hypogonadism 64%
('Mixed' or hypogonadotrophic Hypogonadism)

Prevalence of Klinefelter's Syndrome Diagnosis by Age

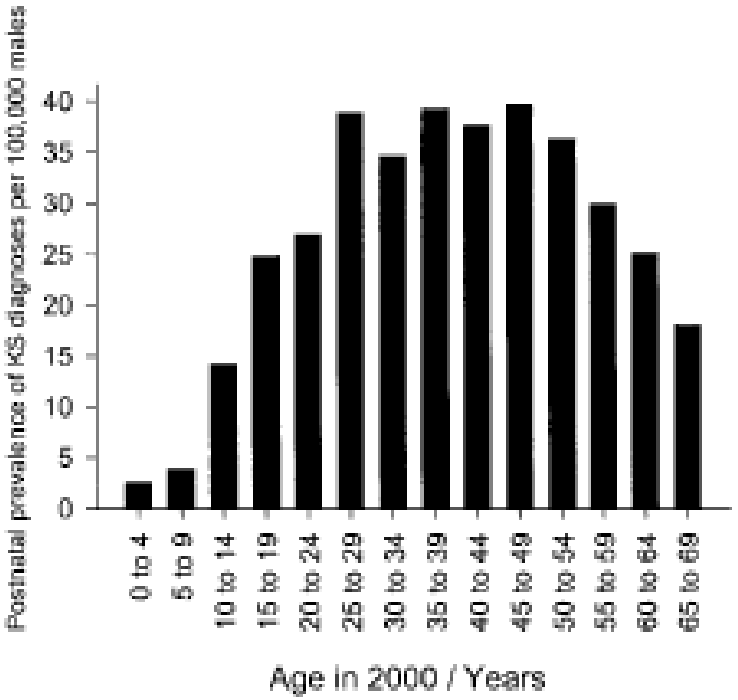


FIG. 1. Postnatal prevalence of KS diagnosis per 100,000 males in the year 2000 in 5-yr age groups (age in the year 2000). The reference prevalence is 153 per 100,000 males.

Bojeson A. et al. JCEM 2008, 88; 622-6

Cardiovascular and Metabolic Risk
ORIGINAL ARTICLE

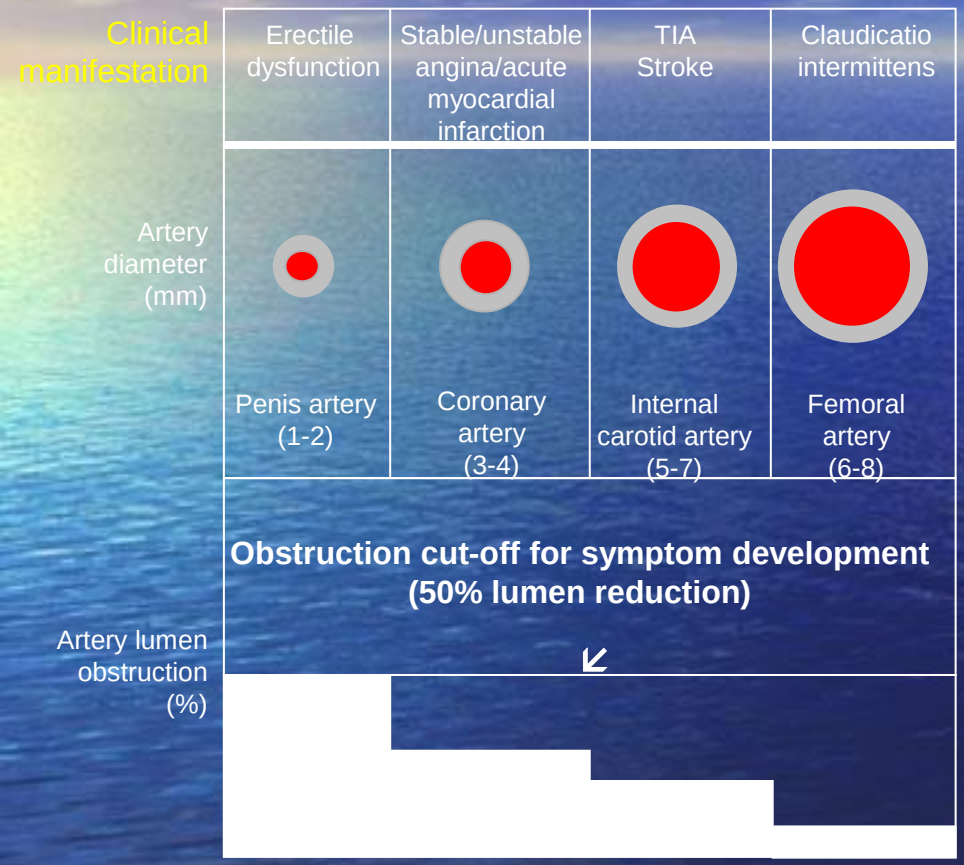
The Metabolic Syndrome Is Frequent in Klinefelter's Syndrome and Is Associated With Abdominal Obesity and Hypogonadism

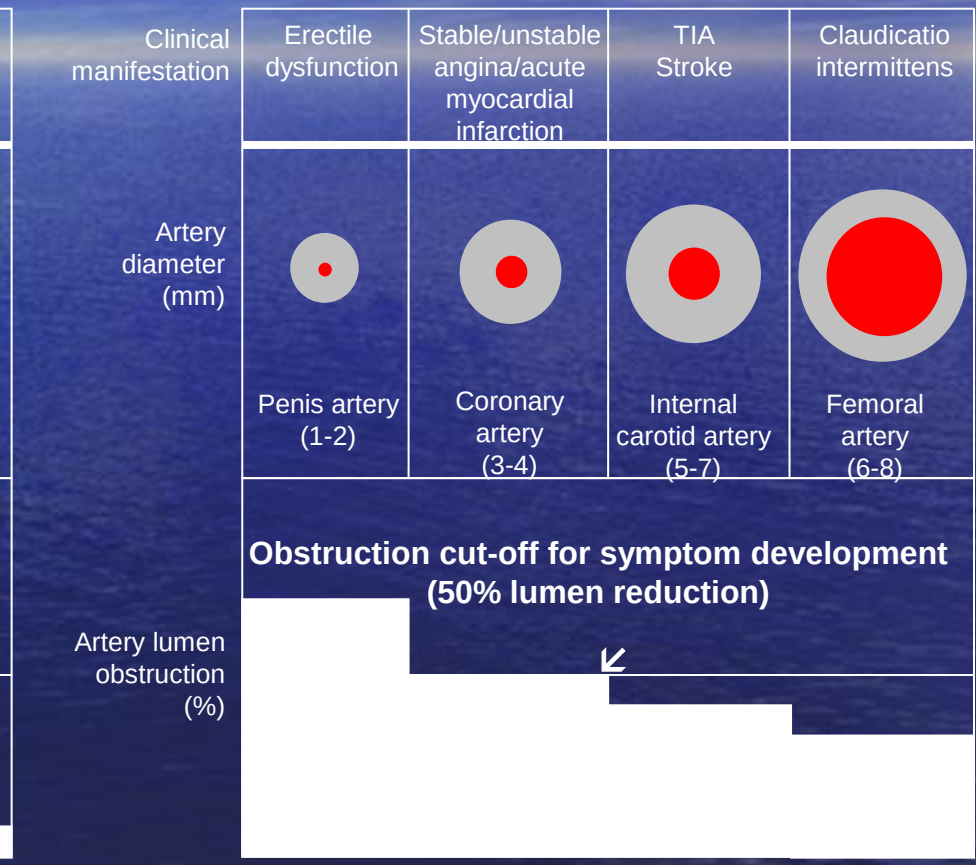
ANDERS BOJESEN, MD, PHD[1,2]
KURT KRISTENSEN, MD, PHD[3]
NIELS H. BIRKEBAEK, MD, PHD[3]
JENS FEDDER, MD, PHD[4]
LEIF MOSEKILDE, MD, DMSCI[5]
PAUL BENNETT, MD[6]
PETER LAURBERG, MD, DMSCI[7]
JAN FRYSTYK, MD, DMSCI[1]
ALLAN FLYVBJERG, MD, DMSCI[1]
JENS S. CHRISTIANSEN, MD, DMSCI[1]
CLAUS H. GRAVHOLT, MD, DMSCI[1]

tion, primarily through increased truncal fat and decreased muscle mass. Testosterone treatment in Klinefelter's syndrome only partly corrected the unfavorable changes observed in untreated Klinefelter's syndrome, perhaps due to insufficient testosterone doses.

Diabetes Care 29:1591–1598, 2006

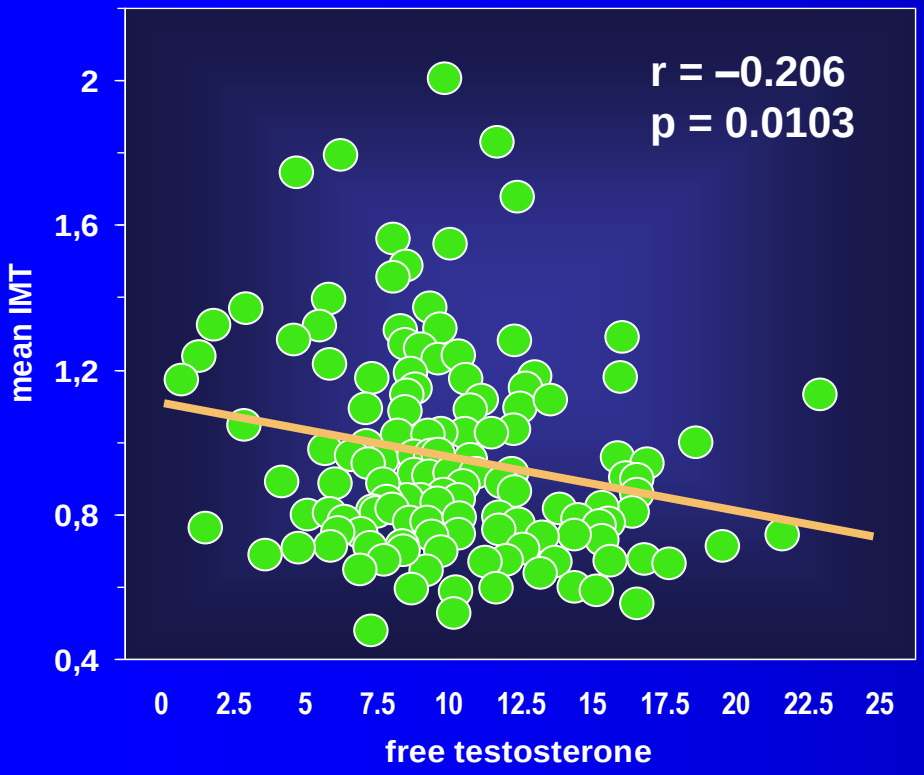
Common Grounds for Erectile Dysfunction and Coronary Artery Disease – Early and Late Steps of the Atherosclerotic Process



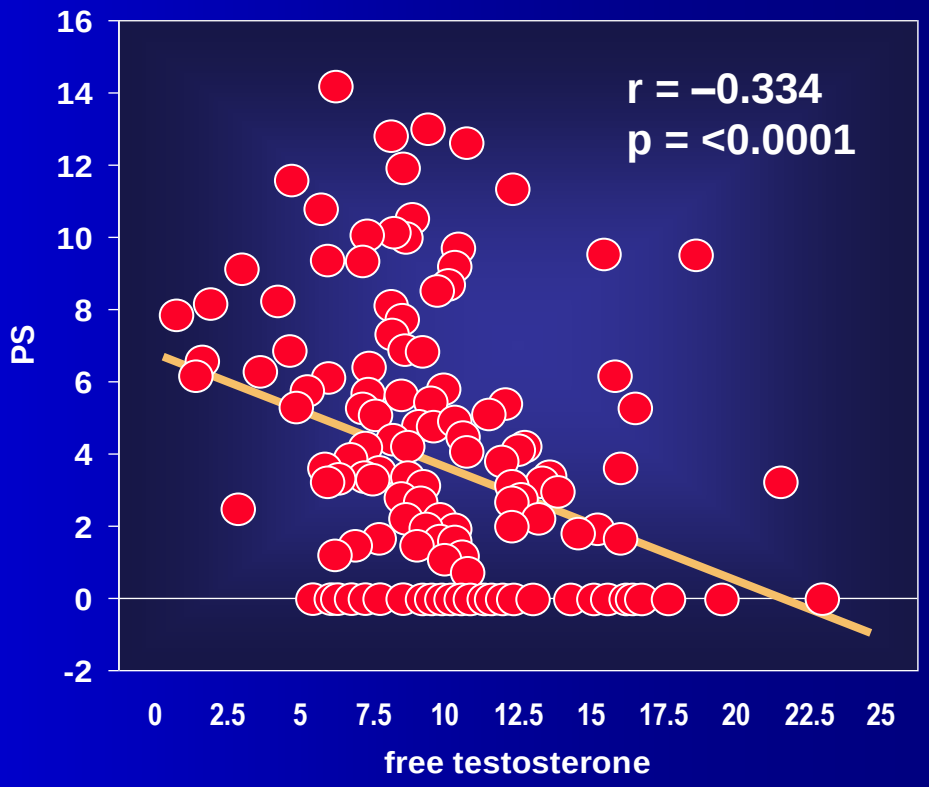


Montorsi P et al. Curr Opin Urol 14: 361-365 (2004)

Association between Free Testosterone and Carotid Atherosclerosis in Men with Type 2 Diabetes (n=154)



IMT: intima media thickness

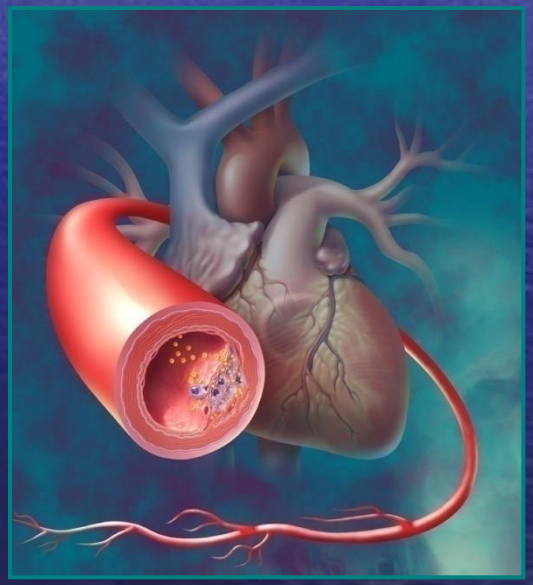


PS: plaque score

Fukui M et al. Diabetes Care 26(6): 1869-1873 (2003)

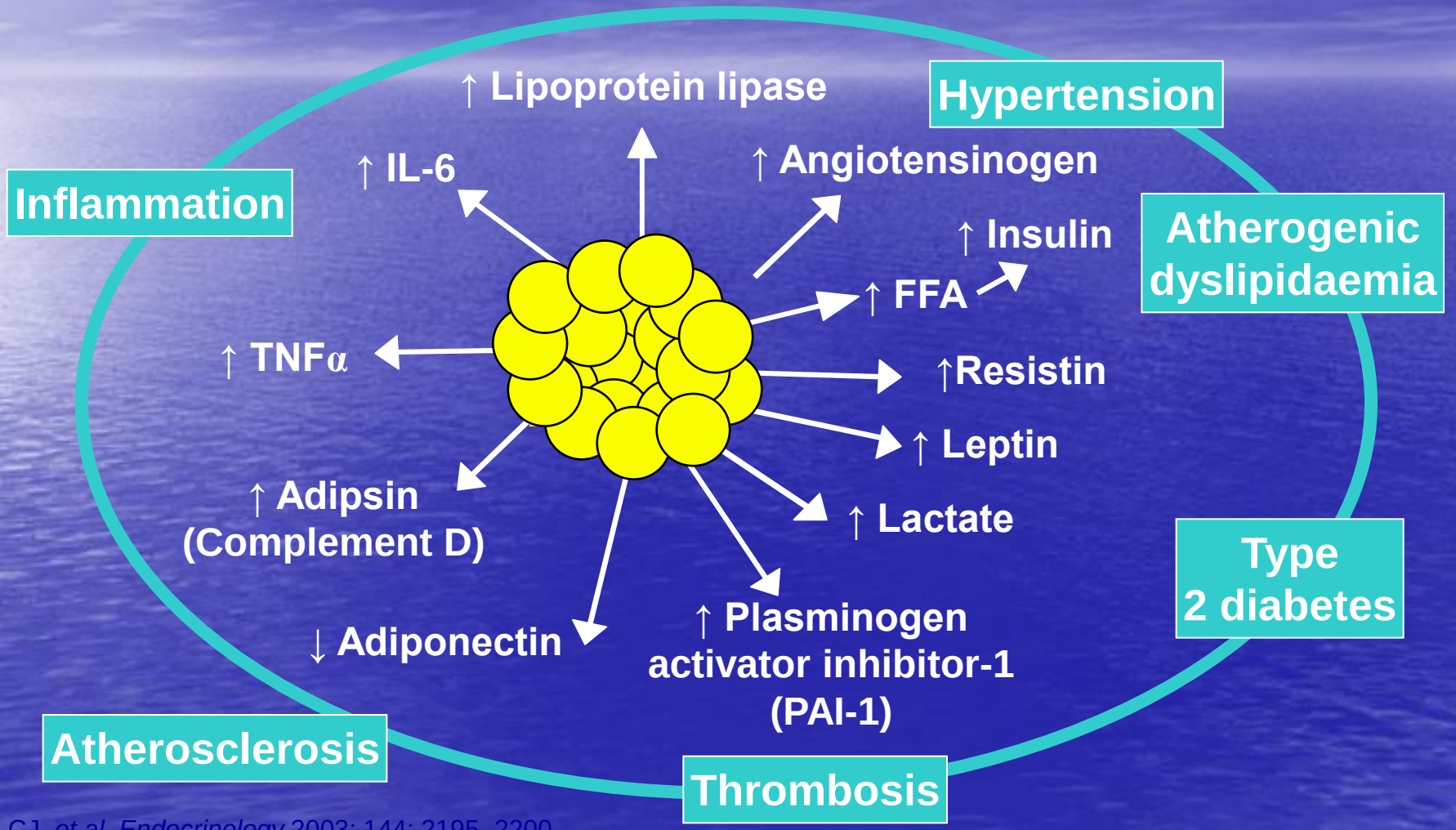
Association of Modifiable Cardiovascular Risk Factors with Testosterone Deficiency

- Visceral Obesity
- Insulin Resistance/Diabetes
- Dyslipidaemia
- Hypertension
- Coagulation
- Inflammation



OBESITY AND INSULIN RESISTANCE

Visceral fat is an active endocrine organ



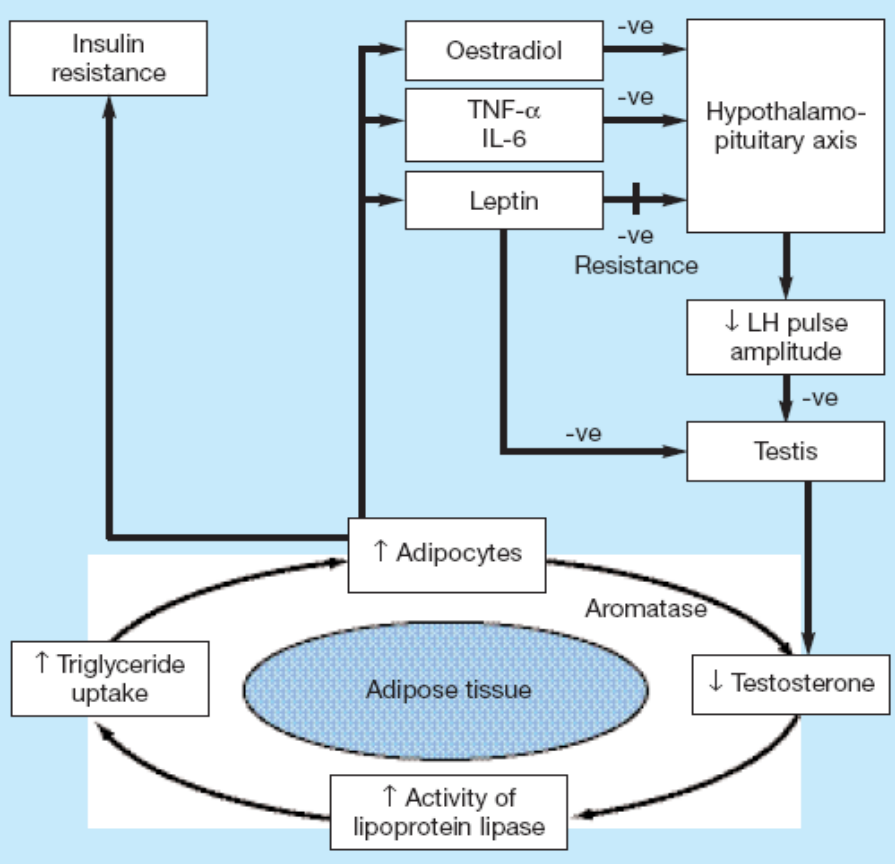
Lyon CJ, *et al. Endocrinology* 2003; 144: 2195–2200.
Trayhurn P, *et al. Br J Nutr* 2004; 92: 347–355.
Eckel RH, *et al. Lancet* 2005; 365: 1415–1428.

Effect of Rosiglitazone (8mg o.d) on testosterone Levels in men with Type 2 Diabetes

	0	2 months	4 months	6 months	p value
HbA_{1C} (%)	8.27±0.3	7.42±0.2	6.91±0.2	7.1±0.2	<0.0001
FBG (mmol/L)	10.68±0.7	8.35±0.9	6.9±0.5	8.28±0.6	0.0002
TT (nmol/L)	10.07±0.5	12.08±1	12.97±0.9	12.52±0.9	0.002
SHBG (nmol/L)	28.94±4.8	38.51±7.6	33.64 ±6.2	37.51±8.9	0.03
Bio T (nmol/L)	3.42±0.19	3.77±0.26	4.15±0.24	3.9±0.19	0.007
Free T (nmol/L)	0.237±0.02	0.246±0.02	0.284±0.03	0.249±0.02	0.01

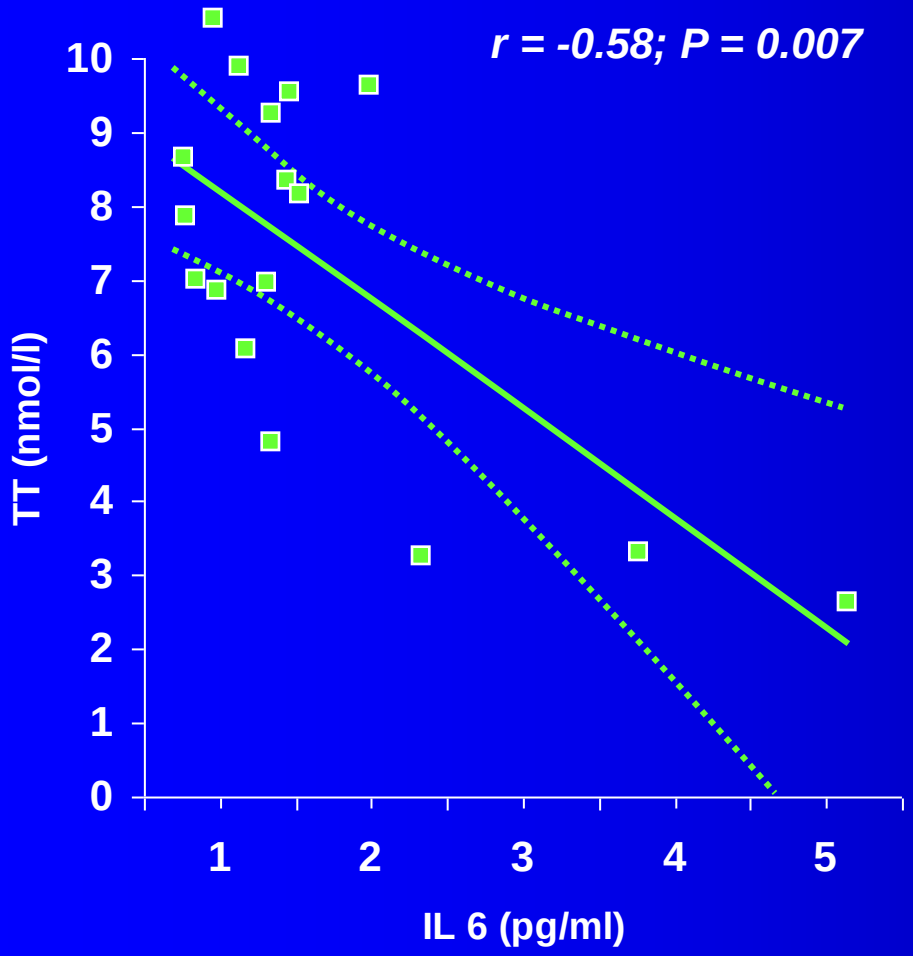
Kapoor D, et al, Diabetes Vasc Dis Res 2008; 5:135-137

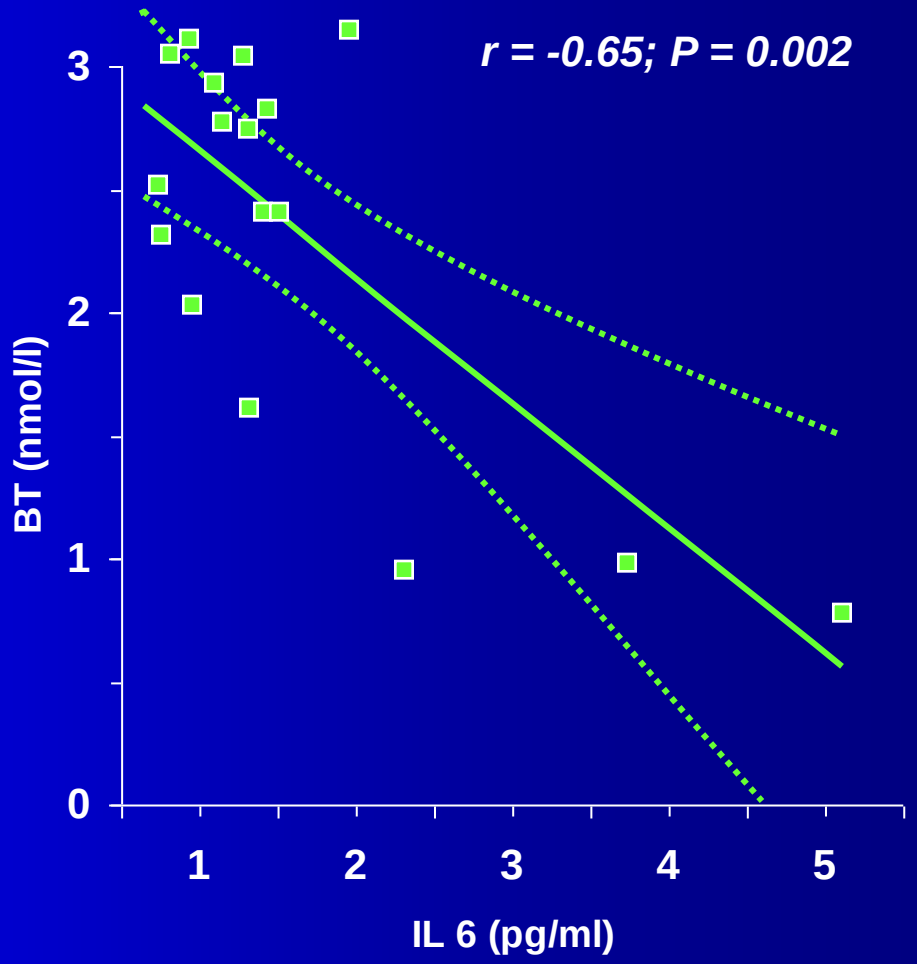
Hypogonadal – Obesity – Adipocytokine Hypothesis



Jones TH Eur Urol 2007 6;847-857

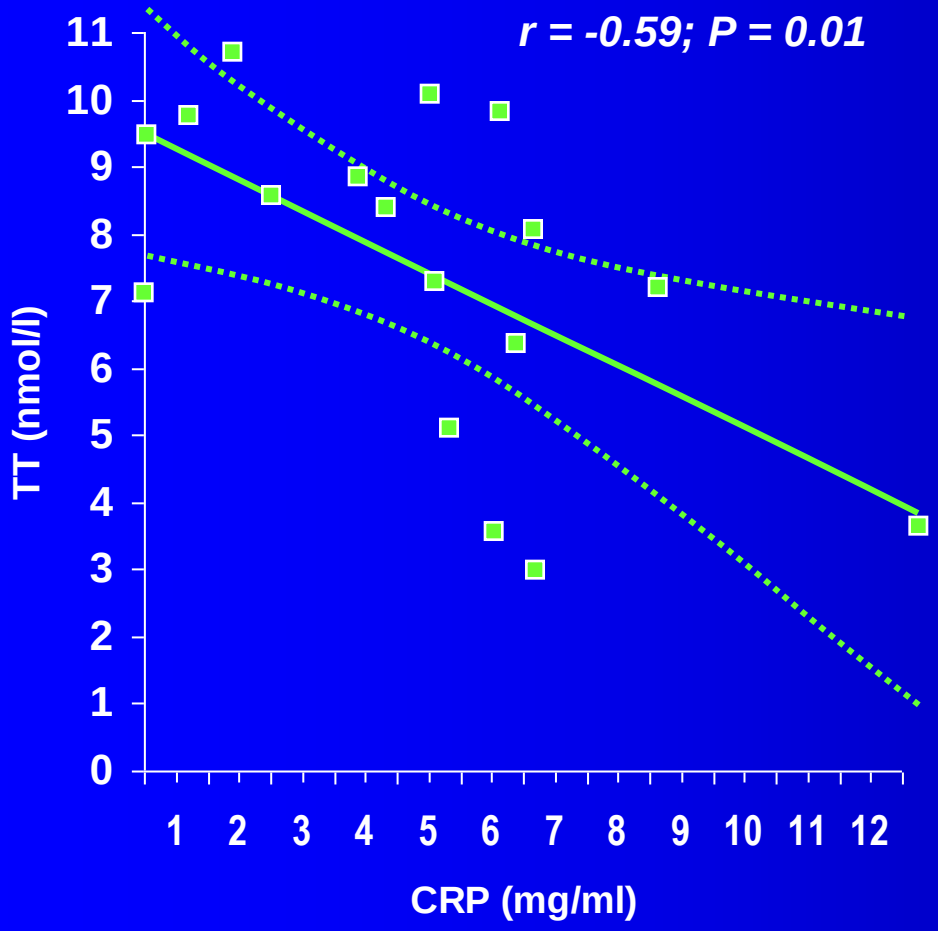
Correlations between IL-6 and Total Testosterone and between IL-6 and Bioavailable Testosterone

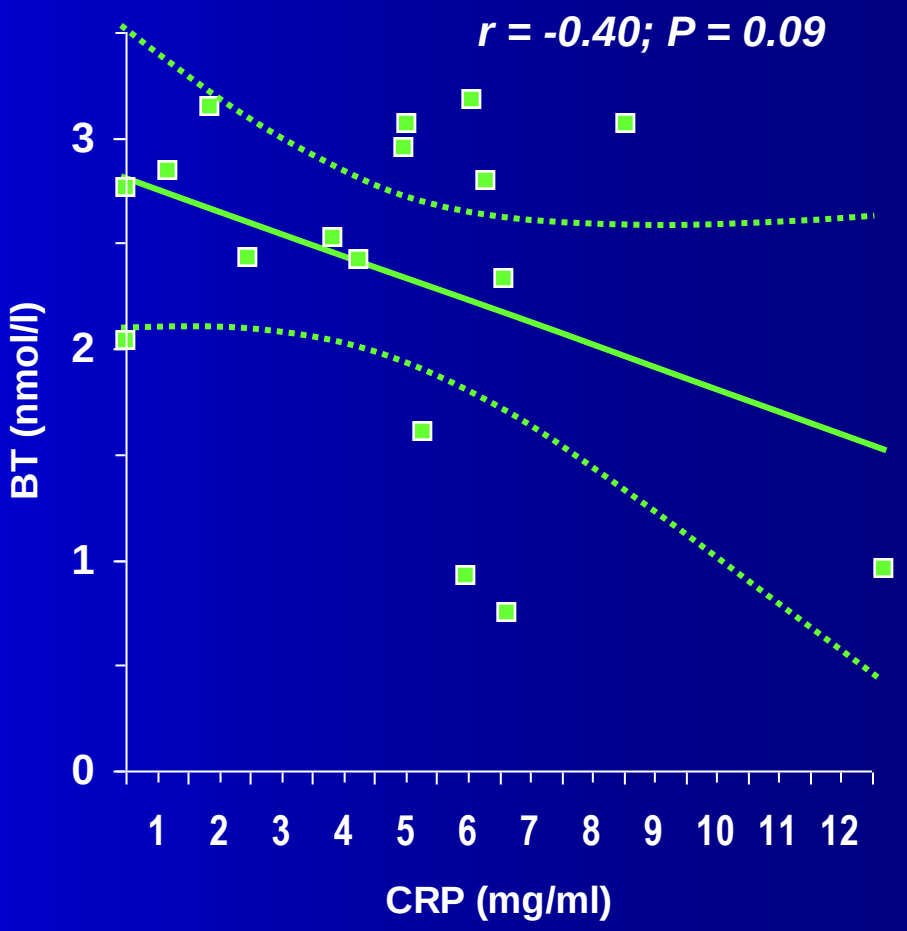




Kapoor D et al. Eur J Endocrinol 156: 595–602 (2007)

Correlations between C-reactive Protein (CRP) and Total Testosterone and between CRP and Bioavailable Testosterone





Kapoor D et al. Eur J Endocrinol 156: 595–602 (2007)

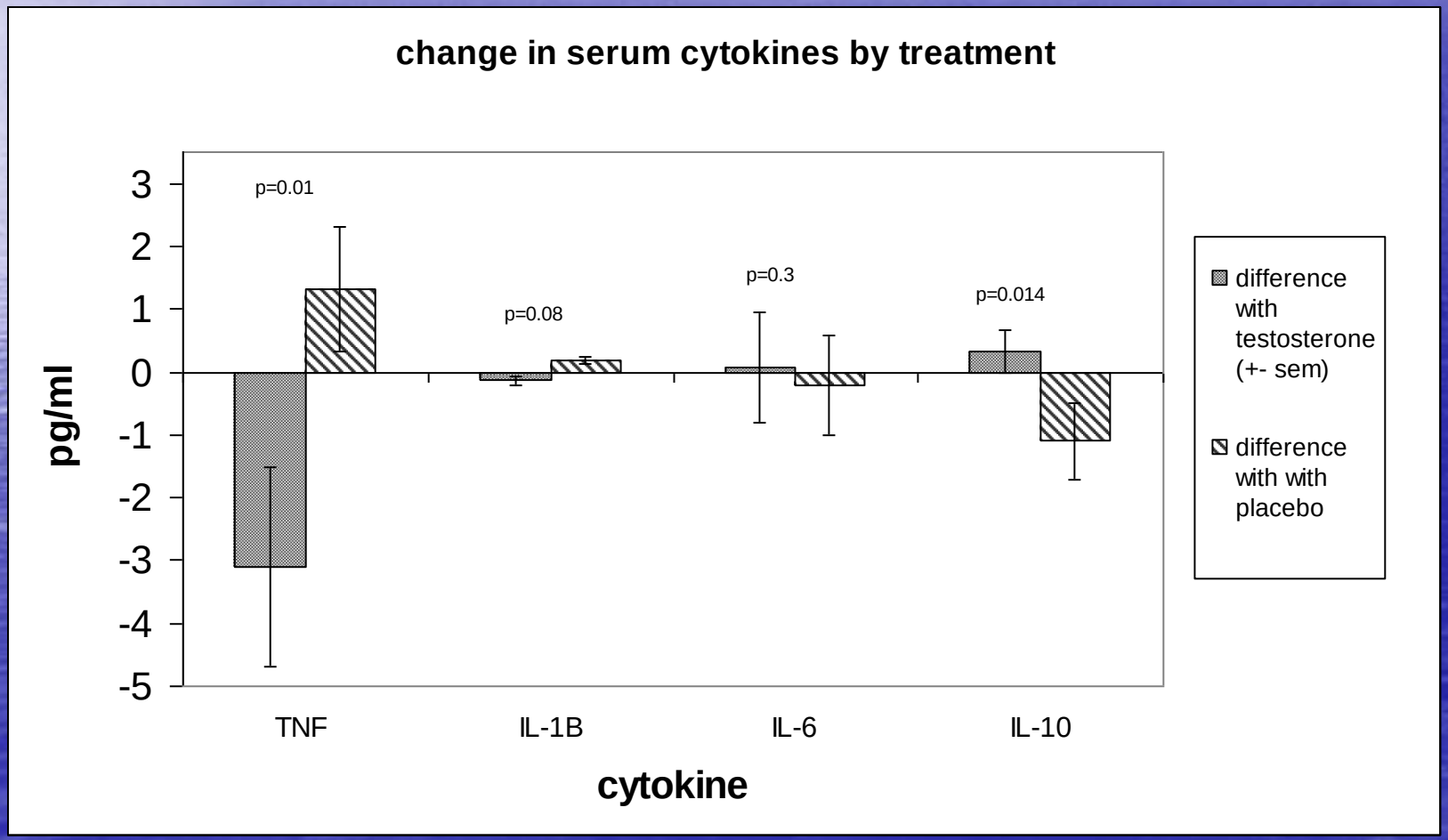
Effects of Androgens on Cytokines

Table 3 Effects of androgens on cytokines

Reference	Androgen	Model	Effect
Chao *et al.* (1995)	T	Rat macrophage	Trend to ↓ TNF production
D'Agostino *et al.* (1999)	T	Mouse marophage	↓ LPS-induced TNF ↑ LPS-induced IL-10
Kanda *et al.* (1996)	T	Human monocytes	↓ IL-6 production
Kanda *et al.* (1997)	T	Human monocytes (patients with systemic lupus erythematosus)	↓ IL-6 production
Li *et al.* (1993)	T	Human monocytes (patients with rheumatoid arthritis and healthy subjects)	↓ IL-1 production
Gornstein *et al.* (1999)	T	Human gingival fibroblasts	↓ IL-6 production
Hofbauer *et al.* (1999)	T	Human osteoblasts	↓ IL-6 production
Hatakeyama *et al.* (2002)	T	Human aortic endothelium	↓ TNF induced VCAM-1 and NFκβ
Araneo *et al.* (1991)	DHT	Mouse cells	↓ γ-interferon, IL-4
Dalal *et al.* (1997)	DHT	Mice with auto-immune disease*	↓ γ-interferon, ↑ IL-10
Kimura *et al.* (1998)	DHEA	Obese rats*	↓ TNF
Ben-Nathan *et al.* (1999)	DHEA	Mice*	↓ IL-1, ↓ LPS-induced TNF
Padgett & Loria (1998)	DHEA	Mouse macrophages	↓ LPS-induced TNF, IL-1, IL-6
Straub *et al.* (1998)	DHEA	Human monocytes	↓ IL-6 production
Spinedi *et al.* (1992)	Castration	Mice*	↑ LPS-induced TNF

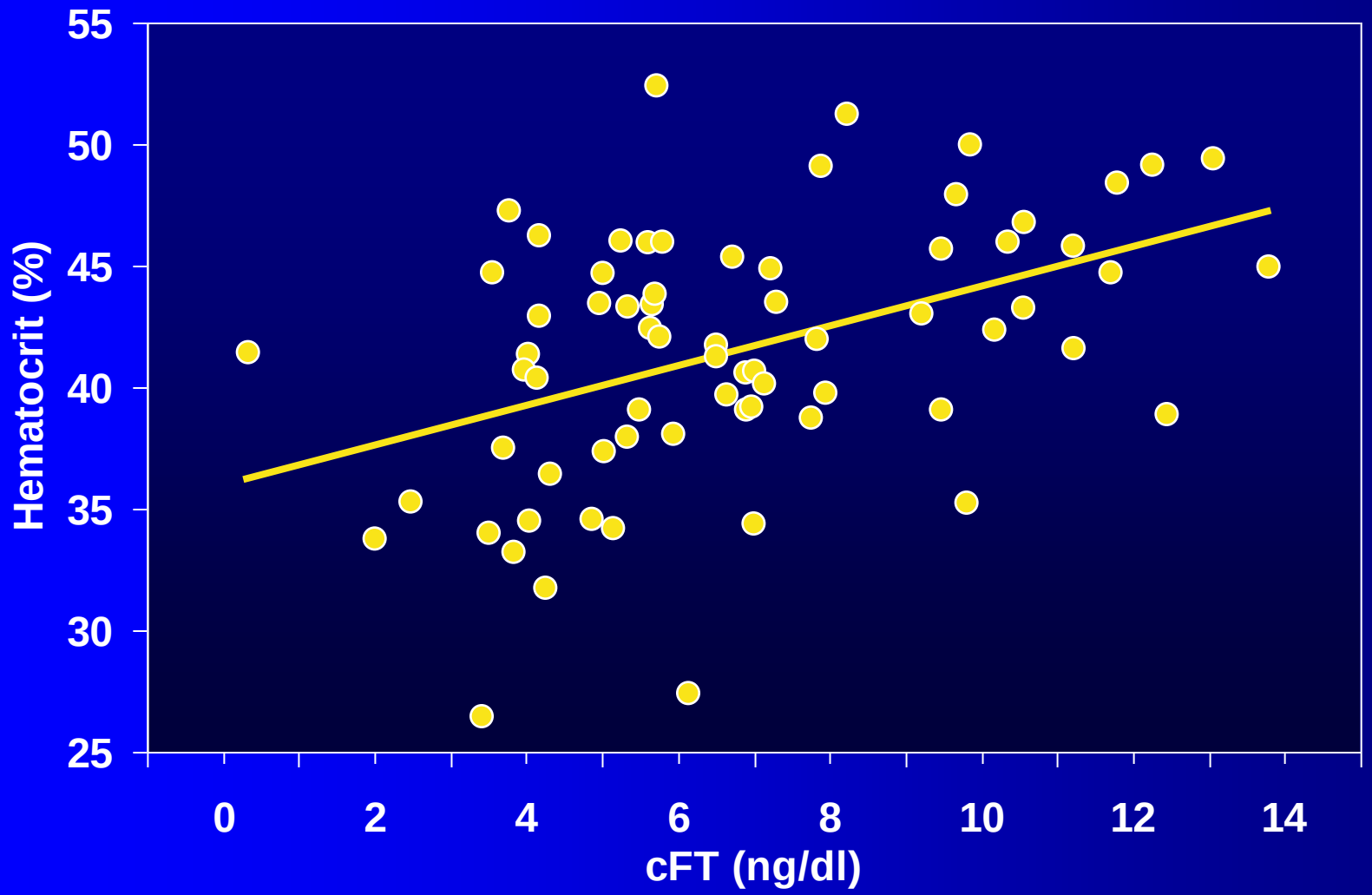
*in vivo. LPS, lipopolysaccharide; T, testosterone; DHT, dihydrotestosterone; DHEA, dehydroepiandrosterone; VCAM-1, vascular cell adhesion molecule 1; IL, interleukin; TNF, tumour necrosis factor; NFκβ, nuclear factor-kappaβ.

Effect of TRT on Serum Cytokine Levels in Men with Hypogonadism



Malkin C et al, JCEM 2004;89:3313

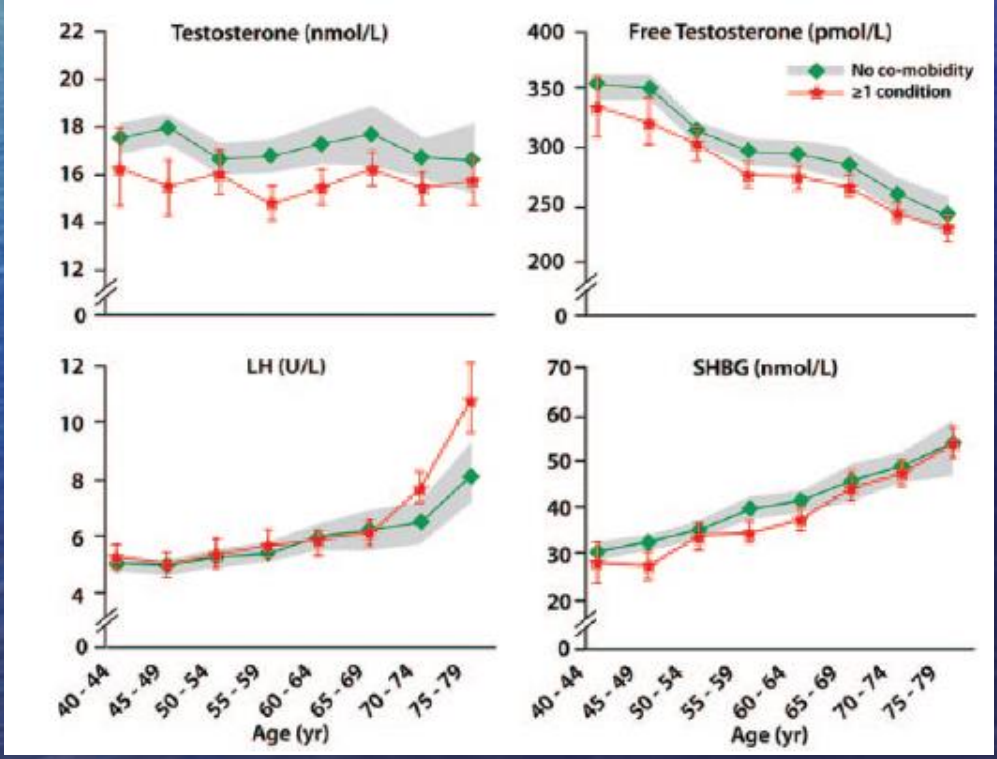
Relationship between cFT and Hematocrit (r=0.46: P<0.0001) in 70 Diabetic Patients. There was also a significant relationship between total testosterone and hematocrit (r=0.36; P=0.002)



Bhatia V et al. Diabetes Care 29: 2289-2294 (2006)

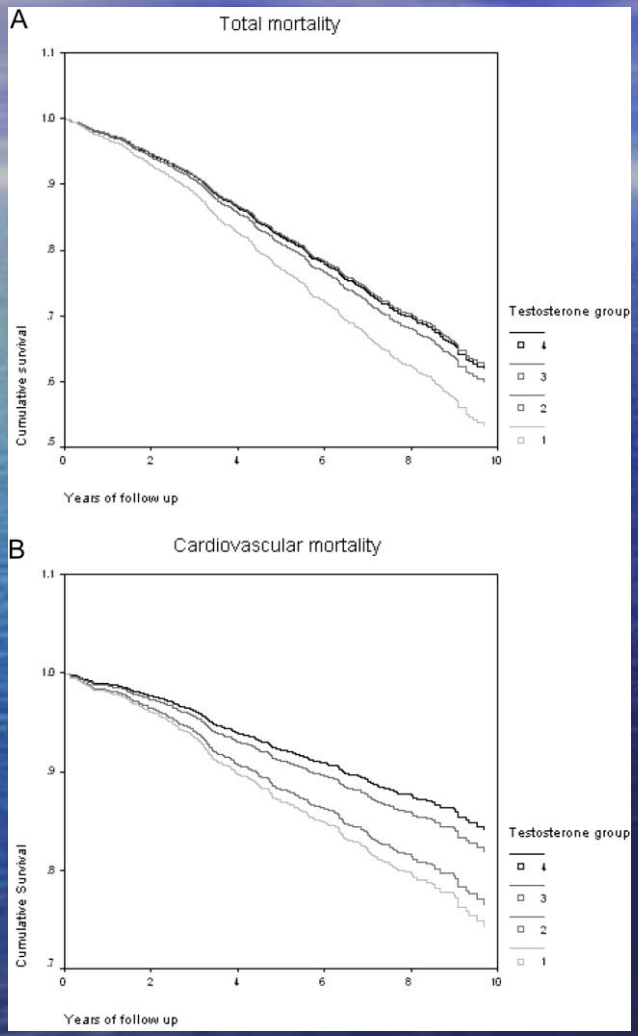
Hypothalamic-Pituitary-Testicular Axis Disruptions in Older Men Are Differentially Linked to Age and Modifiable Risk Factors: The European Male Aging Study

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



Testosterone and Death

Multivariate-adjusted survival by quartile group of endogenous testosterone concentrations (1 is lowest, 4 is highest) in 2314 men 42 to 78 years old in EPIC-Norfolk 1993 to 2003



Quartiles of Testosterone

4 >19.6 nmol/l

3 15.7 – 19.6 nmol/l

2 12.5 – 15.6 nmol/l

1 < 12.5nmol/l

Khaw, K.-T. et al. Circulation 2007;116:2694-2701

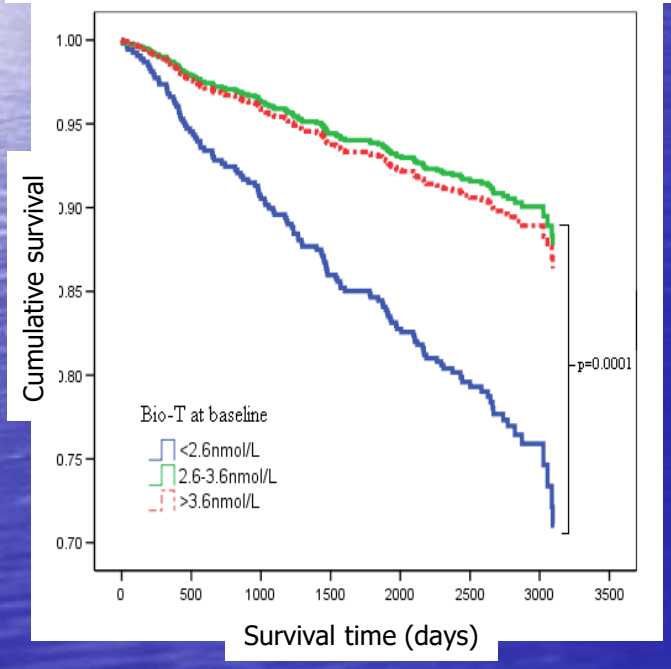
Circulation

American Heart Association®

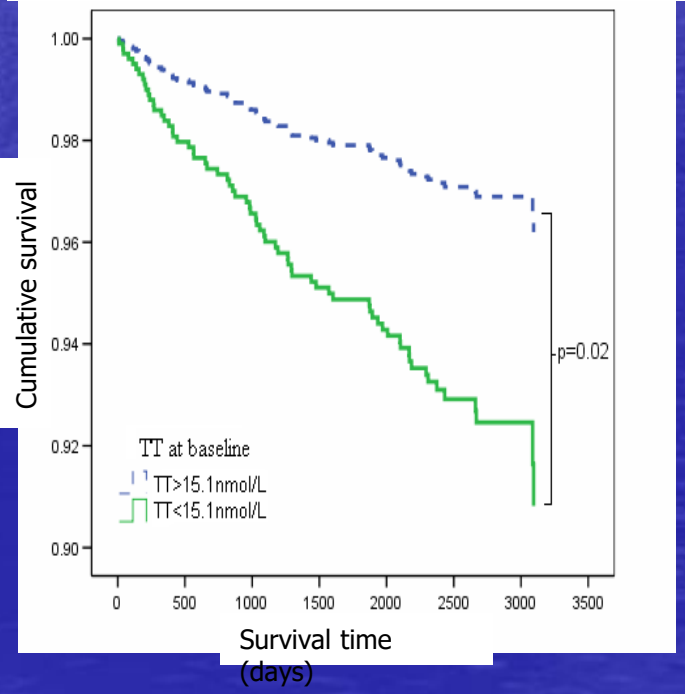
Learn and Live℠

Mortality in Men with Proven Coronary Heart Disease 7 year follow up (n=930)

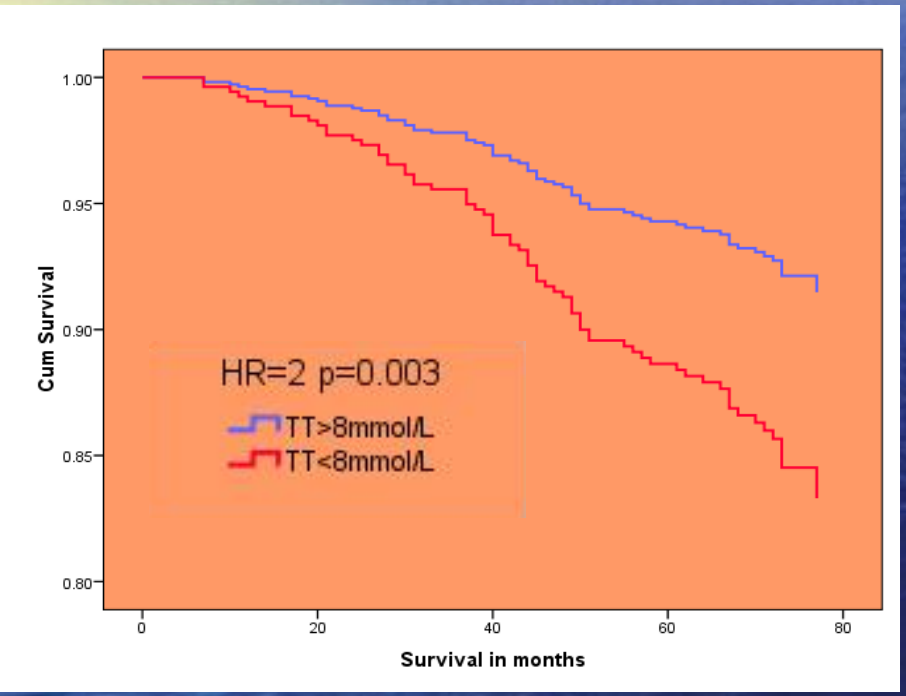
Survival by bio-T status/all cause mortality (adjusted)



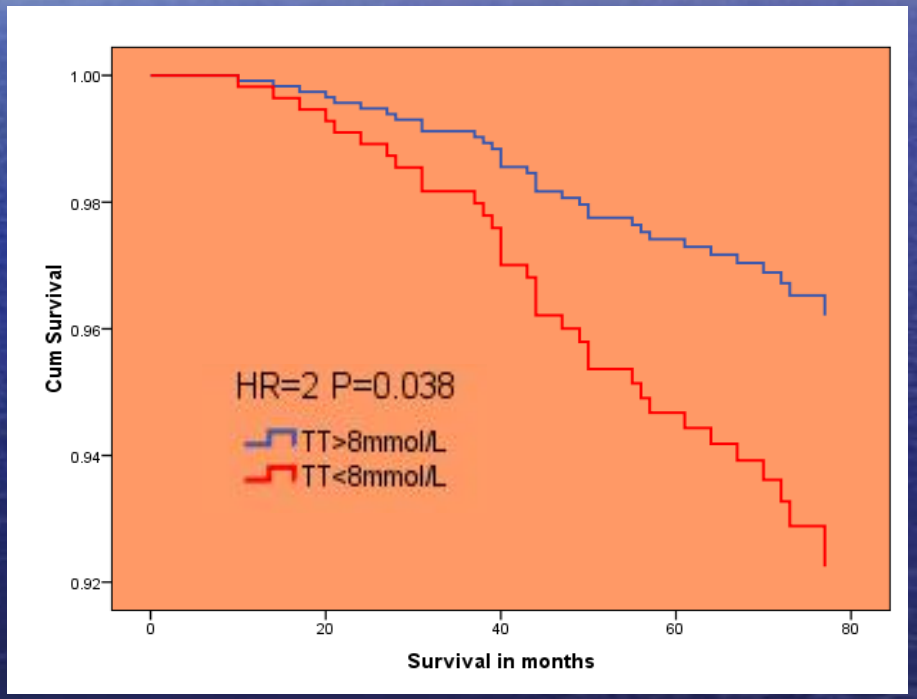
Survival by total testosterone status/vascular mortality



Mortality in Men with Type 2 Diabetes Kaplan-Meier Survival Curves For Normal And Low Testosterone Groups (5 year follow up - Age adjusted, n=587)



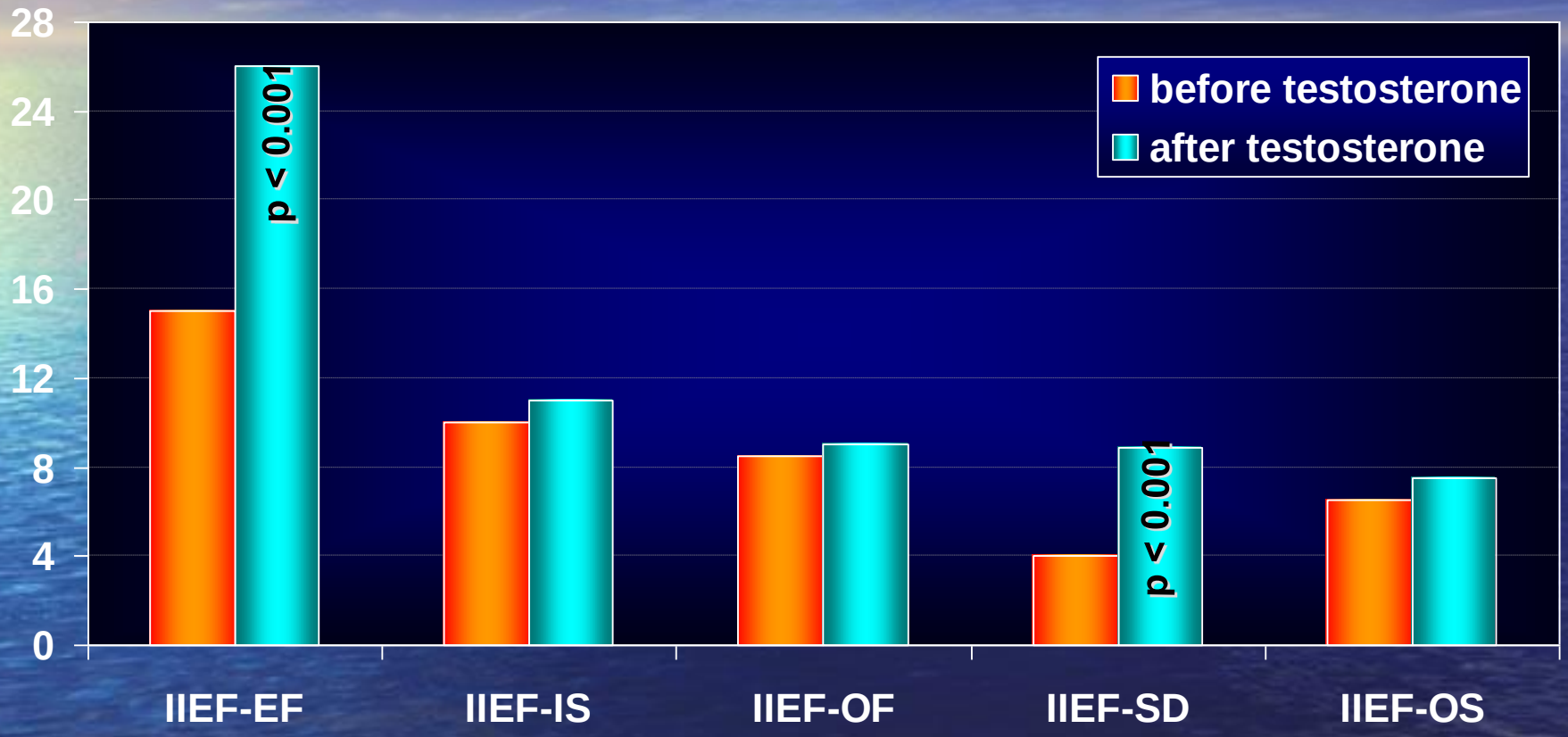
All-Cause Mortality



Cardiovascular Mortality

Evidence for Treatment

Testosterone Alone (Testosterone Gel 5g/d/3 mo) Significantly Improves Erectile Function and Sexual Desire in 31 of 49 Hypogonadal (< 400 ng/dL, ~14 nmol/L) Patients with ED

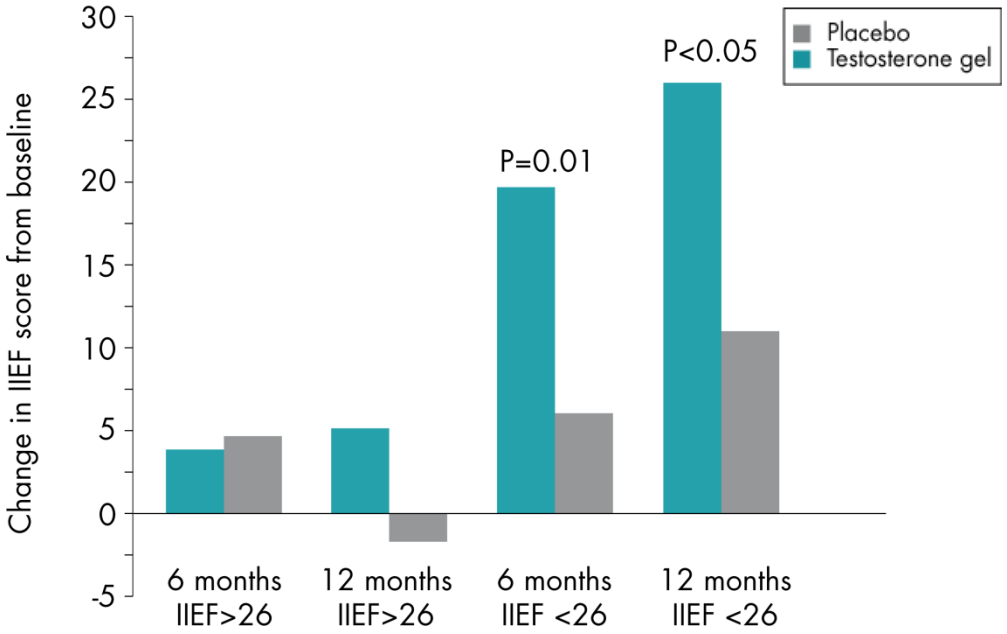


EF erectile function; IS intercourse satisfaction; OF orgasmic function; SD sexual desire; OS overall satisfaction

Greenstein A et al. J Urol 173: 530-532 (2005)

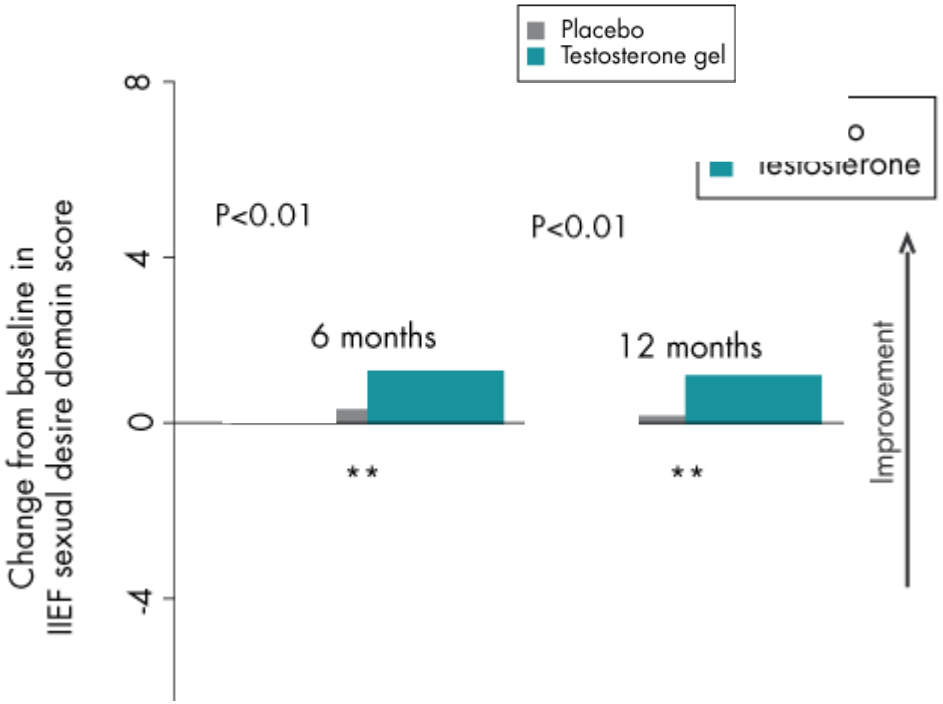
Hypogonadal symptoms – IIEF total score (LOCF)

Mean change in IIEF from baseline by baseline score



Hypogonadal symptoms – IIEF sexual desire domain score (LOCF)

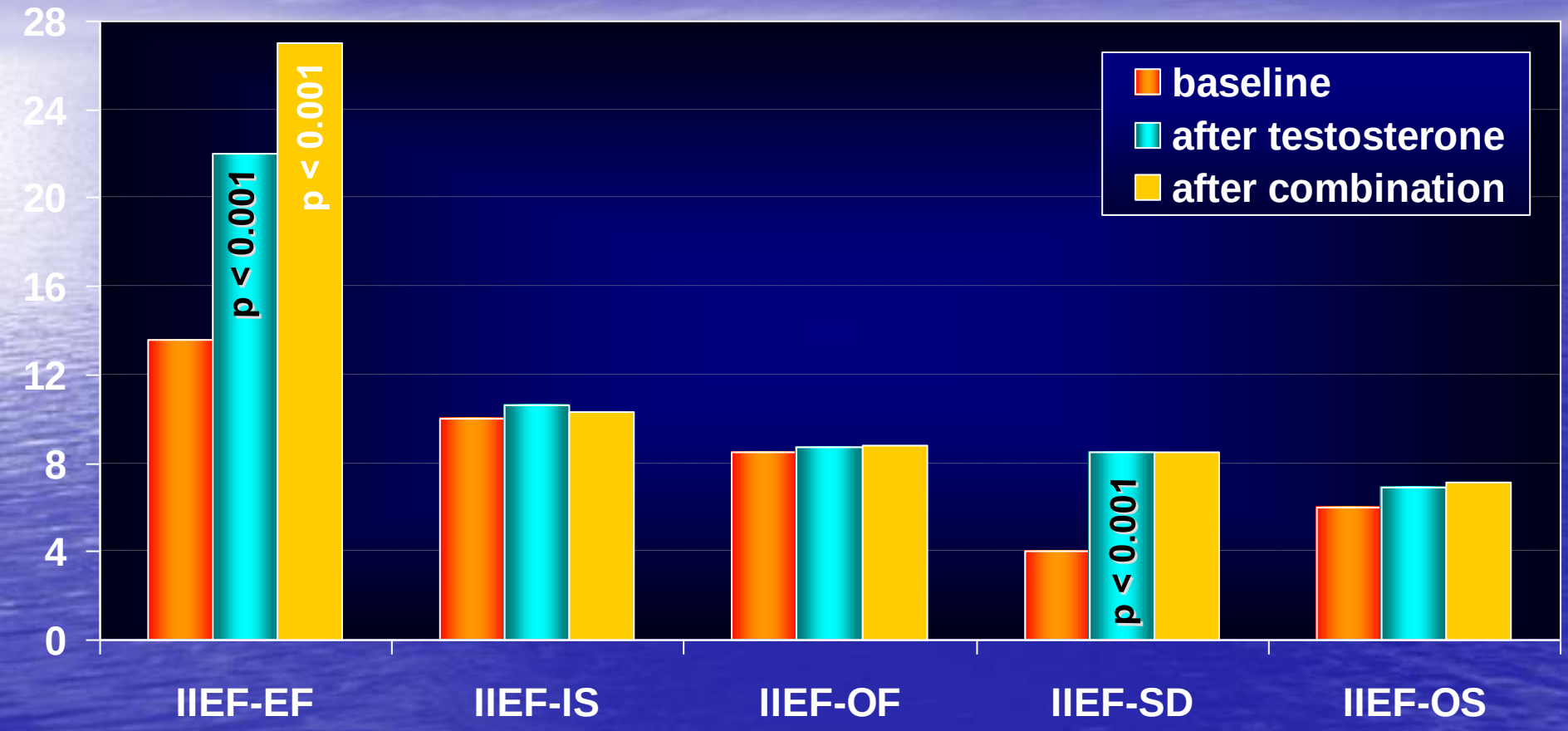
Mean change in IIEF sexual desire domain score from baseline



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

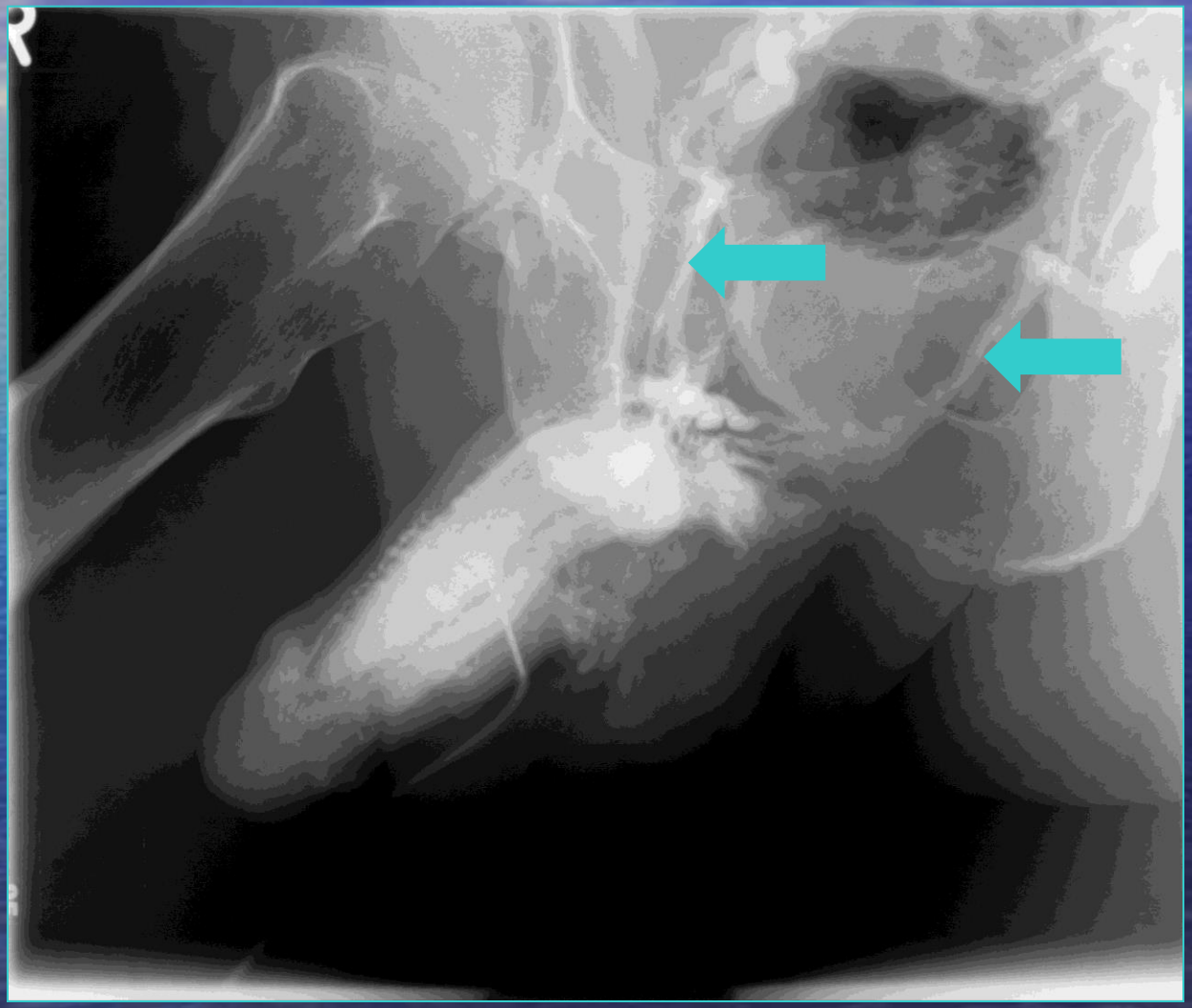
Testosterone in Combination with a PDE5 Inhibitor Significantly Improves Erectile Function in the Remaining 17 of 49 Hypogonadal Patients with Erectile Dysfunction



EF erectile function; IS intercourse satisfaction; OF orgasmic function; SD sexual desire; OS overall satisfaction

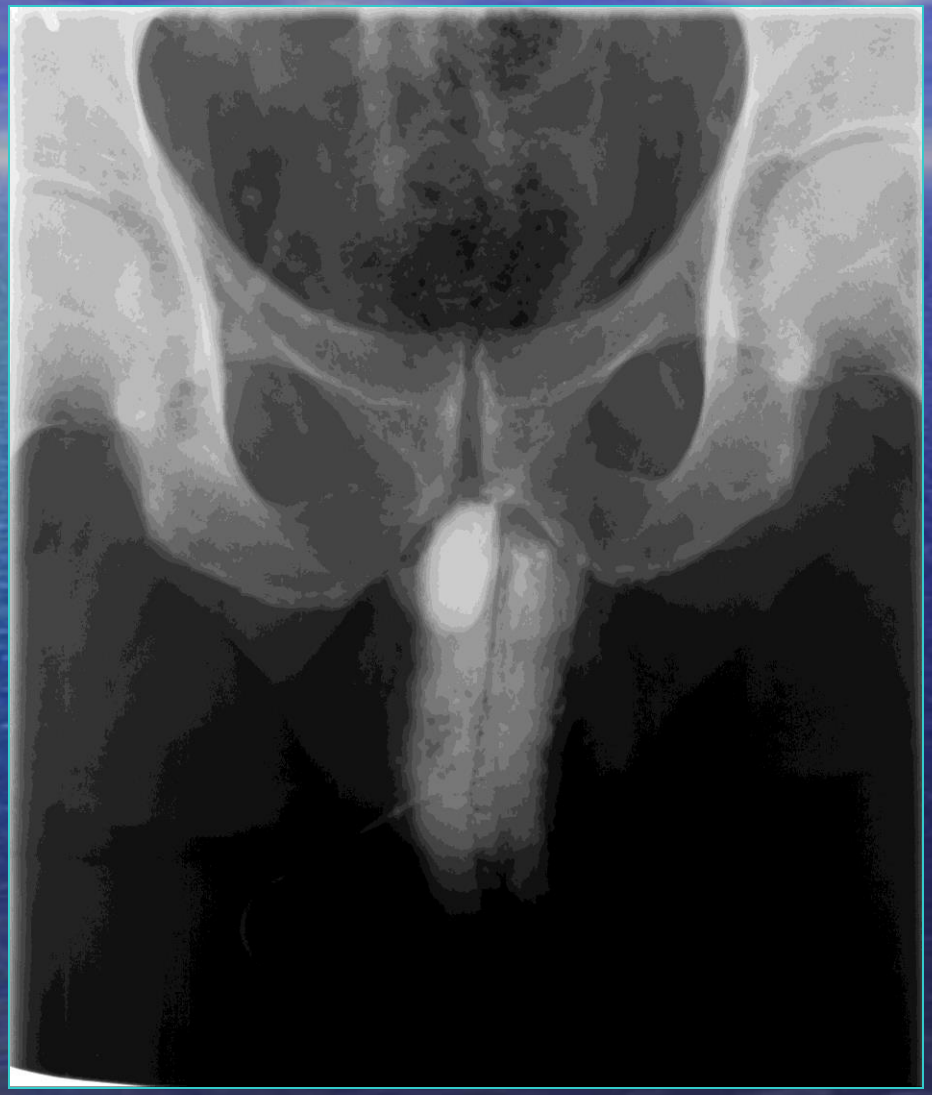
Greenstein A et al. J Urol 173: 530-532 (2005)

Cavernosography in a 56-year-old Hypogonadal Man (T 1.8 ng/mL) with Diabetes Type 2 and ED, Non-Responder to PDE5 Inh. and Alprostadil)



Yassin A and Saad F Andrologia 38: 34-37 (2006)

Cavernosography after 3 mo of Testosterone Therapy (Nebido®)



Yassin A and Saad F Andrologia 38: 34-37 (2006)

Testosterone replacement **I**n hypogonadal men with **Me**tabolic **S**yndrome and type 2 diabetes – the TIMES2 study

Design

- A 12-month analysis of a randomized, double-blind, placebo-controlled study, carried out in eight European countries
- Changes in diabetic and lipid-lowering drugs were prohibited during the first 6 months unless absolutely necessary for clinical management

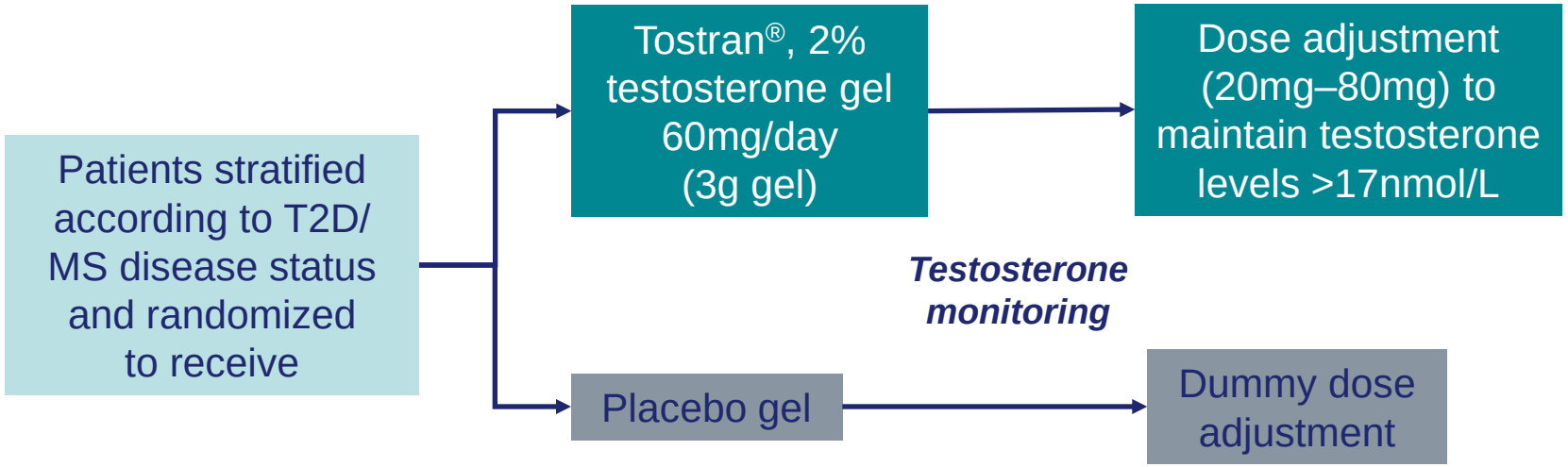
Subjects

- 220 Hypogonadal men (aged ≥40 years) diagnosed with either T2D[1] and/or MS* were eligible for study entry if they had:
  - either a total serum testosterone <11nmol/L or calculated free serum testosterone <255pmol/L
  - at least two symptoms of hypogonadism with no testosterone replacement therapy within the previous 6 months

* MS defined according to International Diabetes Federation Criteria[2]

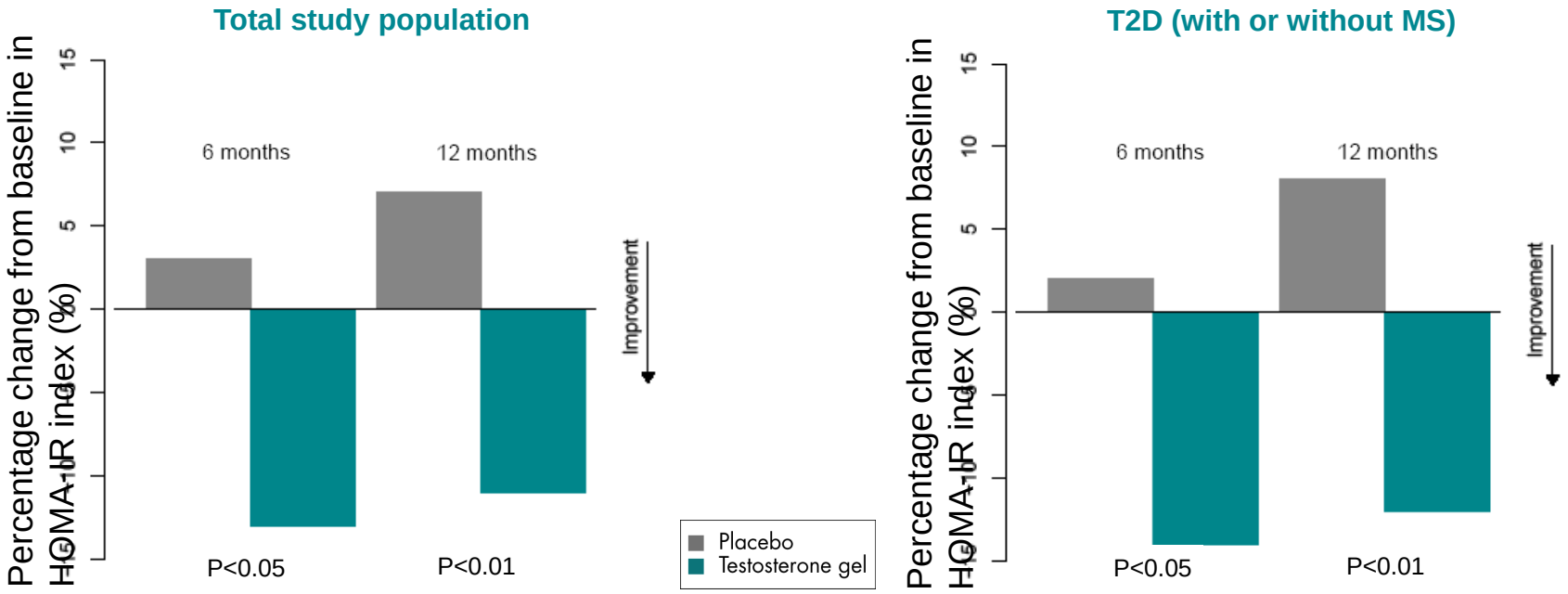
References: 1. Reaven GM. *Physiol Rev* 1995; 75: 473–486. 2. IDF Press Briefing, 1st International Congress on "Prediabetes" and the Metabolic Syndrome, Berlin, Friday 15 April 2005, 0900 (CET).

Interventions



- Changes in diabetes and lipid-lowering medications were prohibited for the first 6 months of the study (unless necessary for appropriate clinical management)

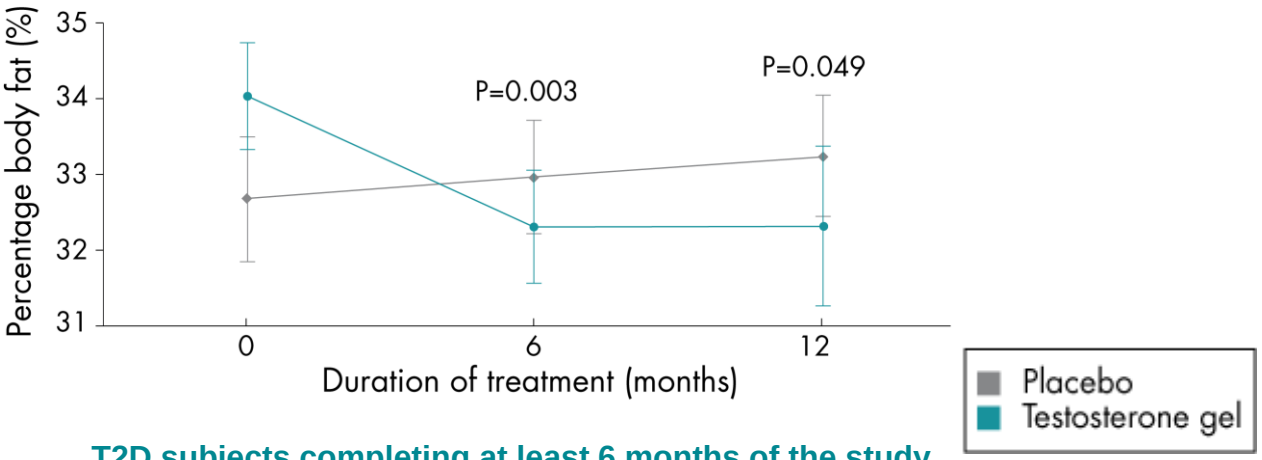
Insulin resistance – HOMA-IR (LOCF) (1)



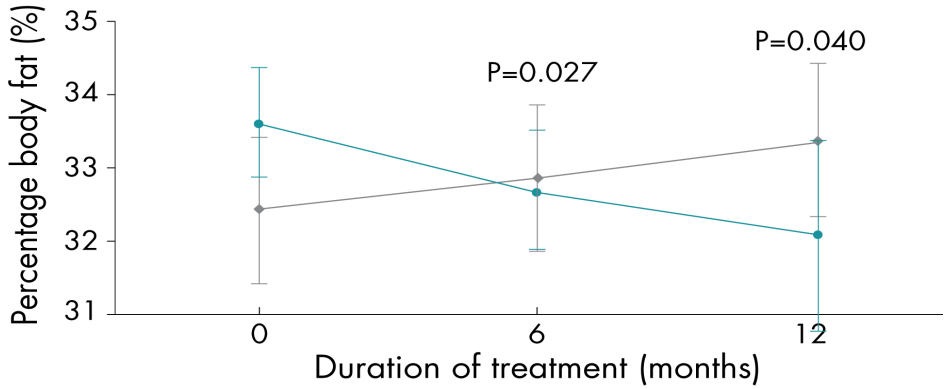
- HOMA-IR significantly improved at 6 and 12 months with testosterone versus placebo in the total study population and in patients with T2D

Percentage body fat (sub-analysis)

MS subjects completing at least 6 months of the study

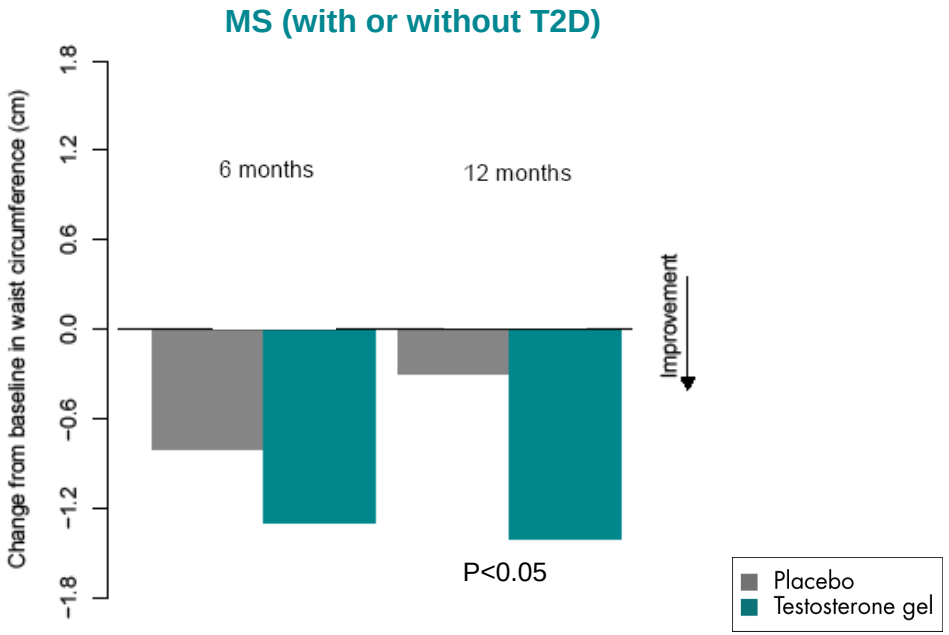


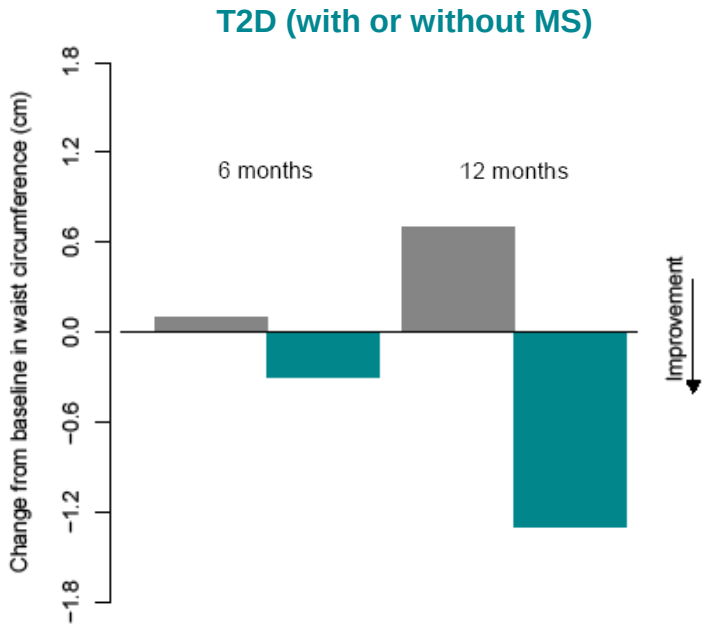
T2D subjects completing at least 6 months of the study



Mean±SEM. *P*-value for change from baseline

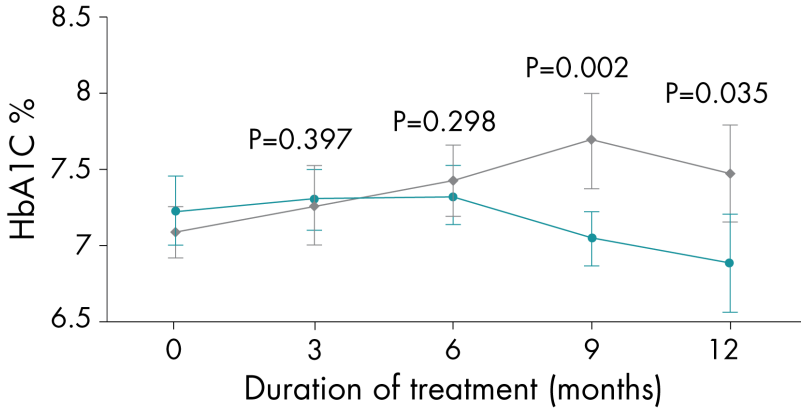
Waist circumference (LOCF)



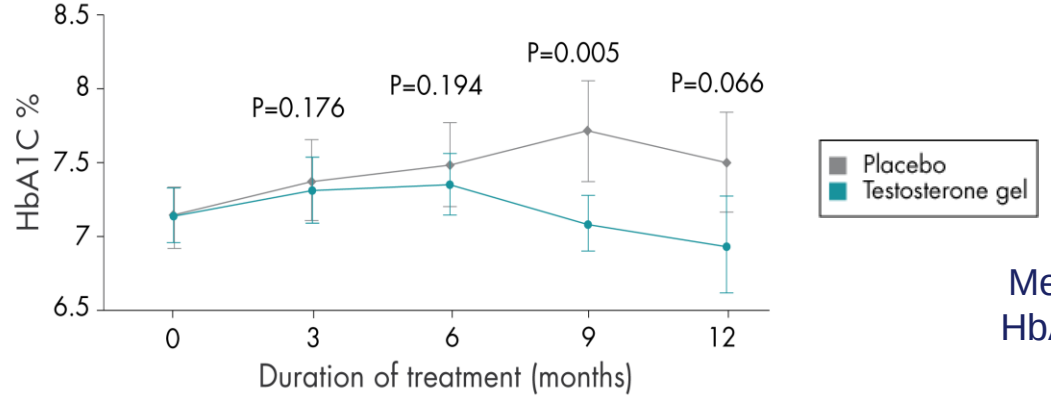


Glycaemic Control – HbA1c

All T2D patients completing at least 6 months of the study (ITT)



All T2D patients completing at least 6 months of the study as per protocol (no change in drugs that affect glycaemic control)

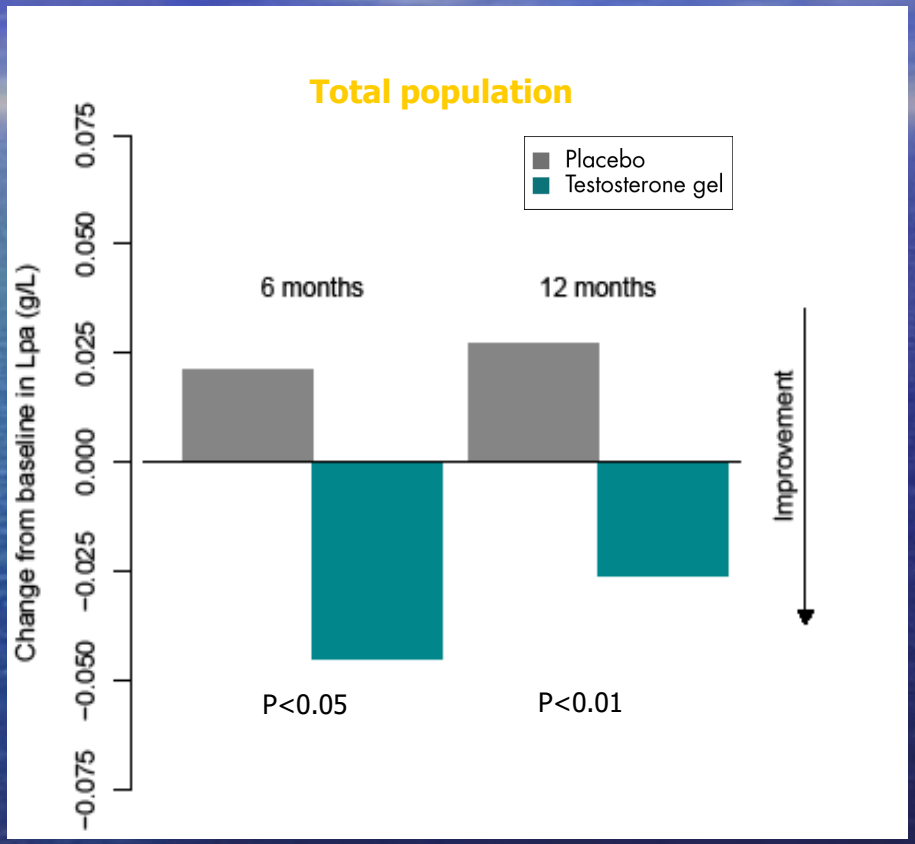


Mean±SEM. *P*-value for difference between treatment groups

Mean difference HbA1c -0.58% at 9 mo.

- In patients with T2D, mean HbA1c was significantly lower in the testosterone group than in the placebo group from month 6 onwards

Lipoprotein a (LOCF)



Consequences of Androgen Deficiency

- Poor Quality of Life
- Loss of Livelihood
- Marital Dysharmony
- Osteopaenia / Osteoporosis
- Debility
- Increased risk of Metabolic syndrome and Type 2 Diabetes
- Risk of Coronary Heart Disease?
- Increased Mortality


COLUMBINE A YEAR LATER:
CAN YOU SPOT A KILLER KID?
STOCKS: IS THIS
DIP DIFFERENT?
TIME
TESTOSTERONE
It restores sex drive.
It boosts muscle mass.
And soon you can get it
as a gel. But it also
can be dangerous.
Is the edge worth it?

Case History

- J.L. 56 yrs
- Erectile dysfunction gradual onset over 2 years. No response to sildenafil.
- No loss of libido or other symptoms of hypogonadism.
- PMH Hypertension, Small CVA
- O/E - Normal

Investigations

- Testosterone 6.2, 8.1, 7.5nmol/l
- LH 21 IU/l
- FSH 37 IU/l

Diagnosis/Management

- Primary Hypogonadism – cause uncertain

- Testogel 50mg
- After 3/12 felt better, improved mood and energy
- Libido excellent
- No improvement in ED
- Testosterone 44.7nmol/l

- Add Tardenafil – Excellent response.
- Repeat Testosterone levels at 6 and 12 months:- 23.9, 25.2 nmol/l.

CONCLUSIONS

- Erectile dysfunction is a well recognised symptom of hypogonadism
- High prevalence of hypogonadism in type 2 diabetes
- Nice Guidelines state that there should be yearly enquiry to the patient on ED
- International guidelines recommend that testosterone be measured in diabetic men with ED

Conclusions

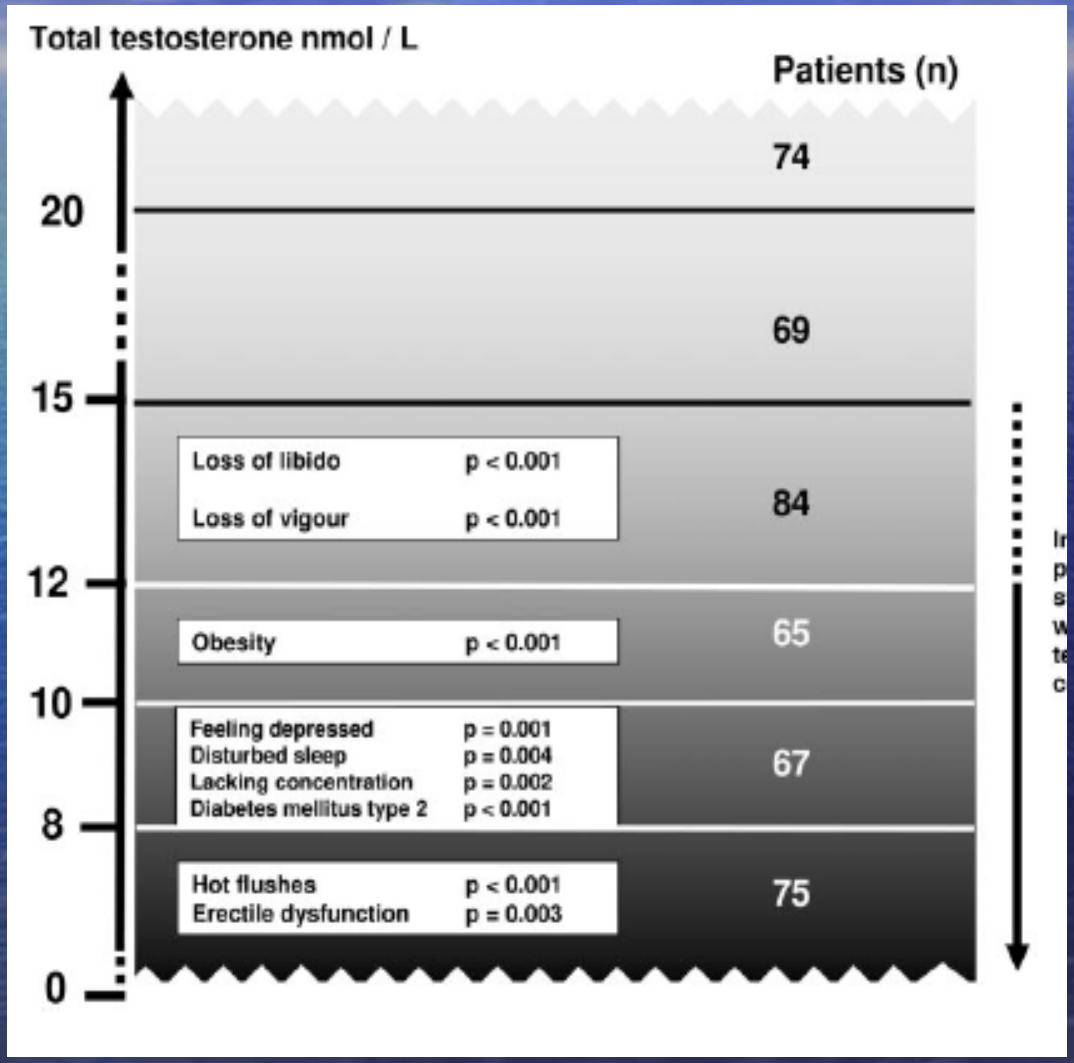
- Low Testosterone is associated with several CV risk factors and the degree of atherosclerosis
- Low T is a marker for early death
- TRT improves several modifiable CV risk factors including insulin resistance

Therefore if you are using NICE guidelines by asking the ED question you are screening for hypogonadism in all Type 2 diabetic men with and without obesity!

‘Medicine is an art based on science’

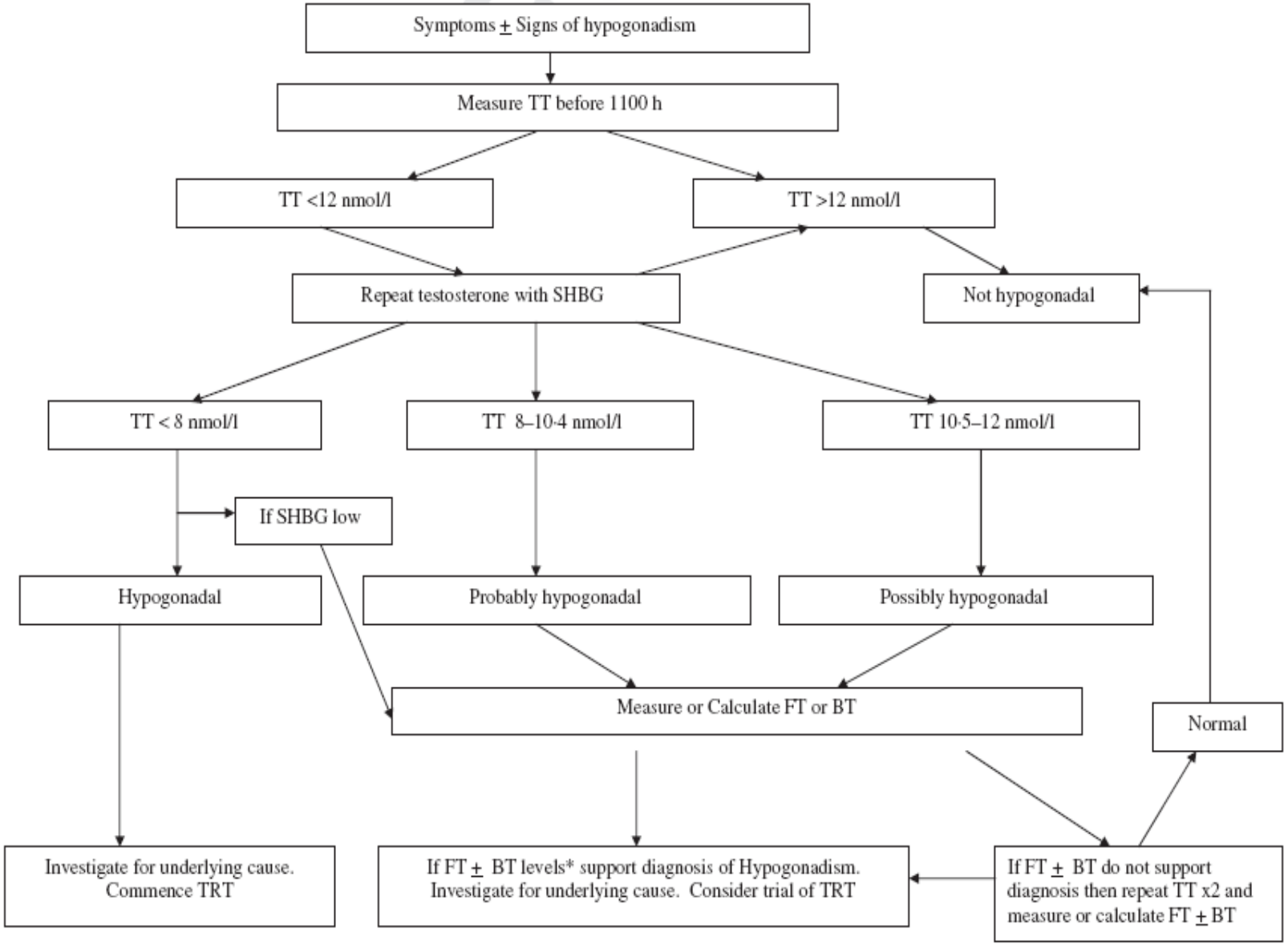
Sir William Osler, 1892

Testosterone deficiency – symptom thresholds



Zitzmann et al. JCEM 2006; 91: 4335–4337.

SUGGESTED ALGORITHM



Late onset hypogonadism

Guidelines exist for diagnosis, but long term studies of treatment are needed

T Hugh Jones consultant physician and endocrinologist and honorary professor of andrology, Robert Hague Centre for Diabetes and Endocrinology, Barnsley Hospital NHS Foundation Trust, Barnsley S75 2EP hugh.jones@nhs.net

Competing interests: THJ has received funding for original investigator led research, given educational lectures, and been a member of advisory boards for drug companies active in this area (Bayer-Schering Pharma, Prostrakan, and Ipsen).

Provenance and peer review: Commissioned; not externally peer reviewed.

Cite this as: *BMJ* 2009;338:b352
doi: 10.1136/bmj.b352

Male hypogonadism is defined as a clinical syndrome complex, which comprises symptoms—with or without signs—and biochemical evidence of testosterone deficiency. Longitudinal population studies show that testosterone concentrations gradually decline with age.[1] One recent study reported the prevalence of hypogonadism to be 4.2% between 30 and 50 years and 8.4% between 50 and 79 years, although other studies have indicated that it may be higher.[2]

The terminology to explain the development of hypogonadism with ageing is controversial. Terms such as male menopause and andropause imply that all men develop this condition, which is not the case. The term late onset hypogonadism has been proposed as a clearer clinical description and is now the preferred terminology of several major international societies.[3] Late onset hypogonadism is defined as "a clinical and biochemical syndrome associated with advancing age and characterised by typical symptoms and a deficiency in serum testosterone levels. It may significantly reduce quality of life and adversely affects the function of multiple organ systems."[3] A diagnosis of late onset hypogonadism can be made only after excluding other causes of hypo-gonadism by appropriate investigation.

Making a diagnosis of late onset hypogonadism, however, is confounded by the syndrome's non-specific symptoms (such as fatigue, loss of motivation and confidence, irritability, and reduced libido and erectile strength). In addition, the most commonly used diagnostic test, total testosterone, can be difficult to interpret. Although total testosterone is a good predictor of hypo-gonadism, it is not a precise assessment of the biologically active fraction in ageing.[1] International guidelines for the diagnosis of this condition have recommended cut-off values for morning total testosterone (0700-1100), on at least two occasions, in the presence of symptoms. Men with values <8 nmol/l usually benefit from testosterone replacement therapy, whereas those with values >12 nmol/l are not hypogonadal.[3,4] Some symptomatic men with low normal values (8-12 nmol/l) may be hypogonadal, so a short (three month) therapeutic trial should be considered.[3,4] The diagnosis of late onset hypogonadism and decisions about treatment should be made by an experienced clinician.

PASIEKA/SPL

The safety of testosterone therapy is constantly questioned, especially regarding the risk of prostate carcinoma. No long term studies have given a definitive answer to this question. A recent analysis of 18 prospective studies found no association between testosterone concentrations and the risk of prostate cancer.[11] Studies of testosterone therapy in older men are small and short term but report no increase in rates of prostate cancer.[12]

Ageing men are at greatest risk of developing prostate cancer and some will be treated for late onset hypogonadism. Guidelines therefore recommend that all men over 45 years are screened for prostate cancer and polycythaemia before starting testosterone

Testosterone Levels in Diabetic Men with and without ED

	With ED	Without ED	P
Total Testosterone (nmol/l)	12.25 ± 0.5	13.14 ± 0.63	0.28
SHBG (nmol/l)	32.26 ± 1.5	27.42 ± 1.8	**0.047**
Bioavailable testosterone (nmol/l)	3.83 ± 0.14	4.46 ± 0.17	**0.006**
Calculated free testosterone (nmol/l)	0.262 ± 0.01	0.303 ± 0.01	**0.027**

Kapoor D et al., Int J Androl 2007

Summary

- Testosterone has several important roles in health and sex:-
- Key player to give libido
- Important in erectile process
- Good cardiac function
- Energy utilisation
- Muscle strength
- Mood