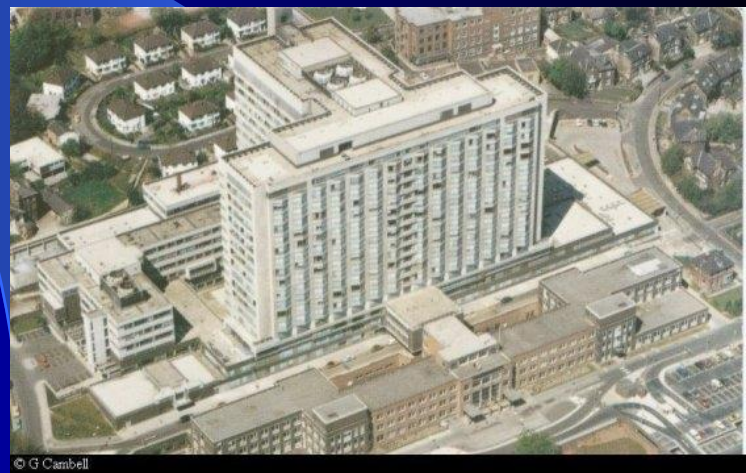
Androgen Replacement Therapy in the Management of Men with Type 2 Diabetes

Hugh Jones

Centre for Diabetes & Endocrinology, Barnsley Hospital NHS Foundation Trust &

Academic Unit of Endocrinology, Division of Genomic Medicine, University of Sheffield Medical School



Sedentary Lifestyle

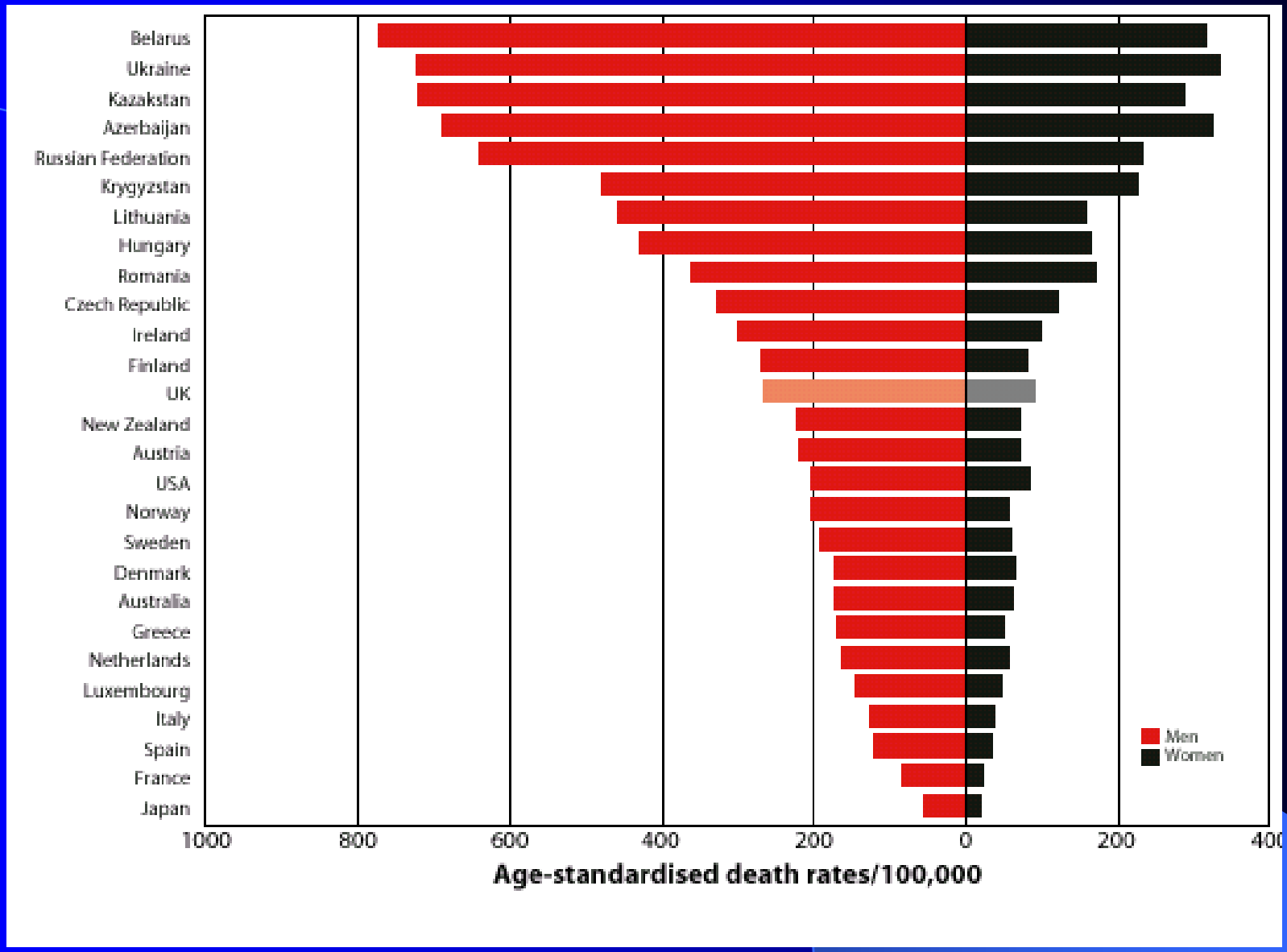

APRIL 24, 2000 $3.50
www.time.com AOL Keyword: TIME
COLUMBINE A YEAR LATER:
CAN YOU SPOT A KILLER KID?
STOCKS: IS THIS
DIP DIFFERENT?
TIME
TESTOSTERONE
It restores sex drive.
It boosts muscle mass.
And soon you can get it
as a gel. But it also
can be dangerous.
Is the edge worth it?

Major Cardiovascular Risk Factors

- Smoking
- Family History
- Diabetes/Metabolic Syndrome
- Hyperlipidaemia
- Hypertension
- Obesity (visceral)
- Lack of Exercise
- Age
- Male Gender

Age adjusted death rates for CAD by country and sex, age 35-74

(British Heart Foundation, Statistics Database 2003)



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

Symptoms of Hypogonadism

- Reduced or loss of Libido
- Reduced strength of erections
- Fatigue
- Loss of Drive
- Reduced Cognitive function
- Sad, grumpy, irritability & depression
- Loss of Physical Stamina
- Increased sweating

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?

Balance of Benefits and Risks of Physiological Testosterone Replacement

- BENEFITS
- Improve QOL
- Save Jobs
- Save Marriages
- ↓ Risk/Treat Osteoporosis
- ↓Visceral Obesity
- ↑ Muscle Strength
- Improves Lipid Profile
- ↓ Coronary Risk?

- RISKS
- Prostate Cancer???
- ↑ Haematocrit

Myth or Reality

Low testosterone levels are fully explained by low levels of SHBG found in men with insulin resistance?

Classically pathway by which testosterone acts "The Genomic pathway"

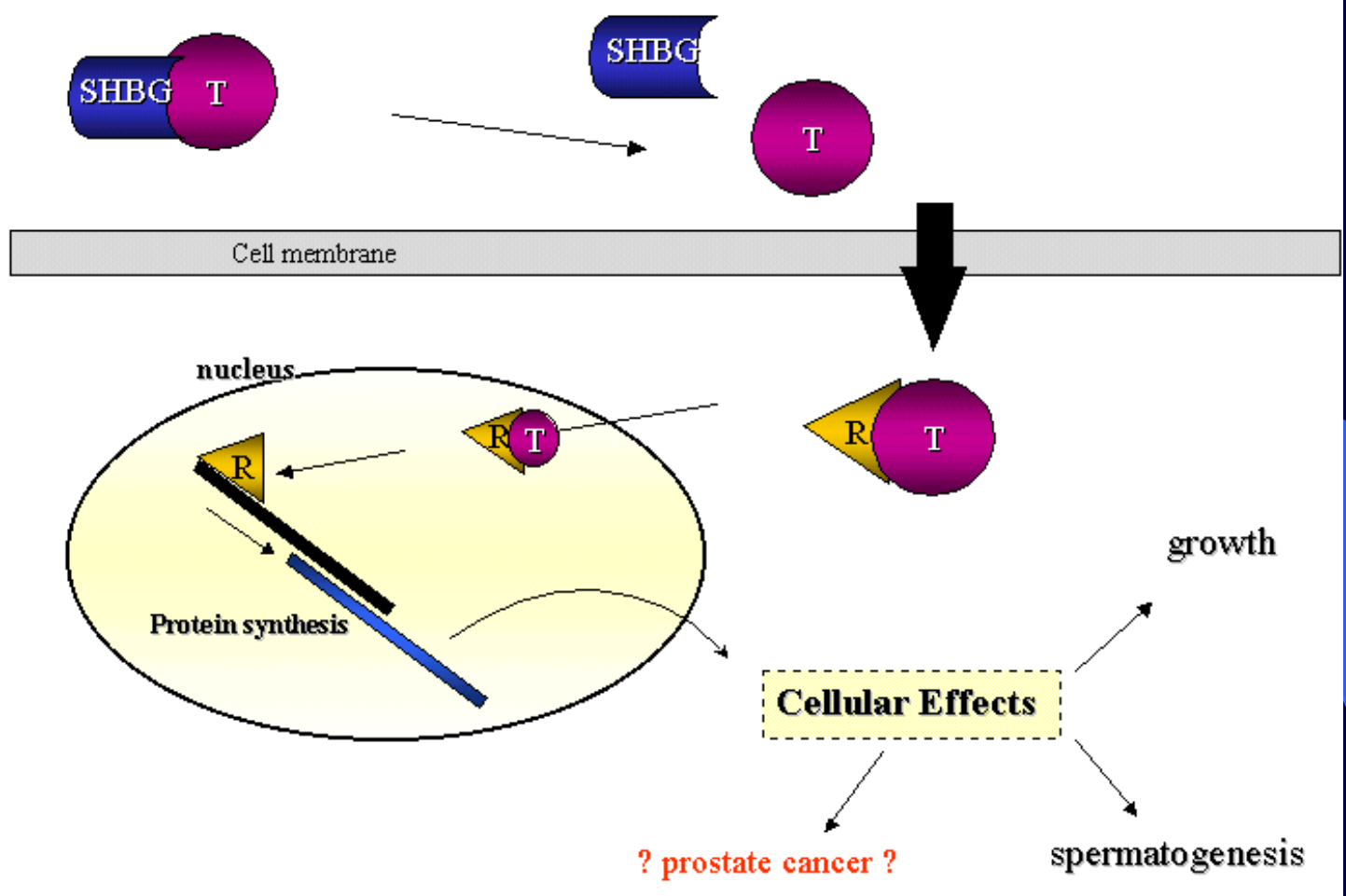
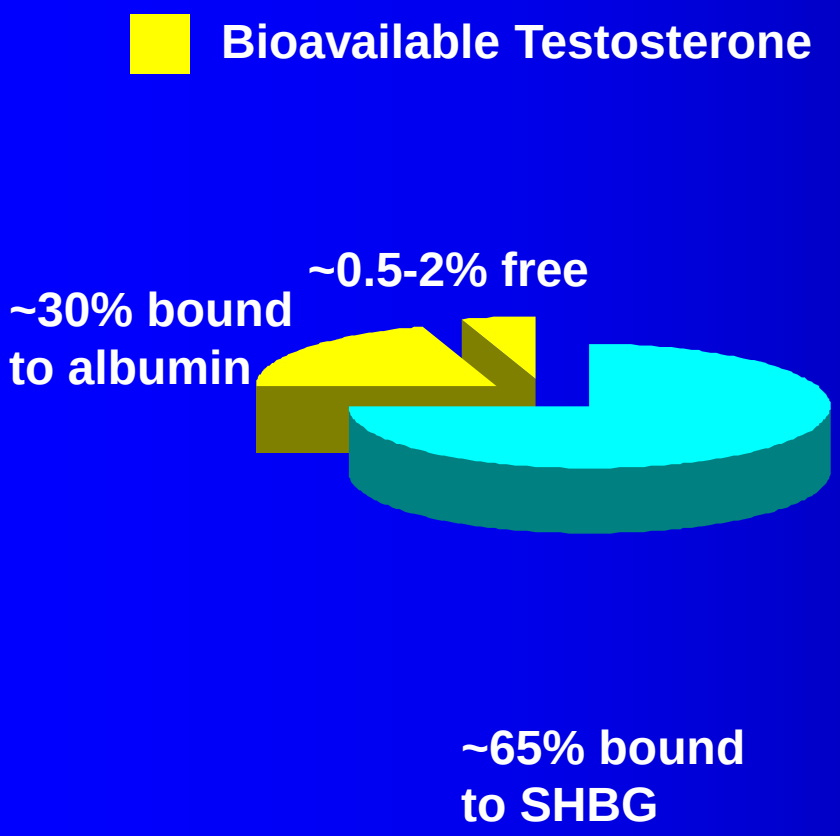
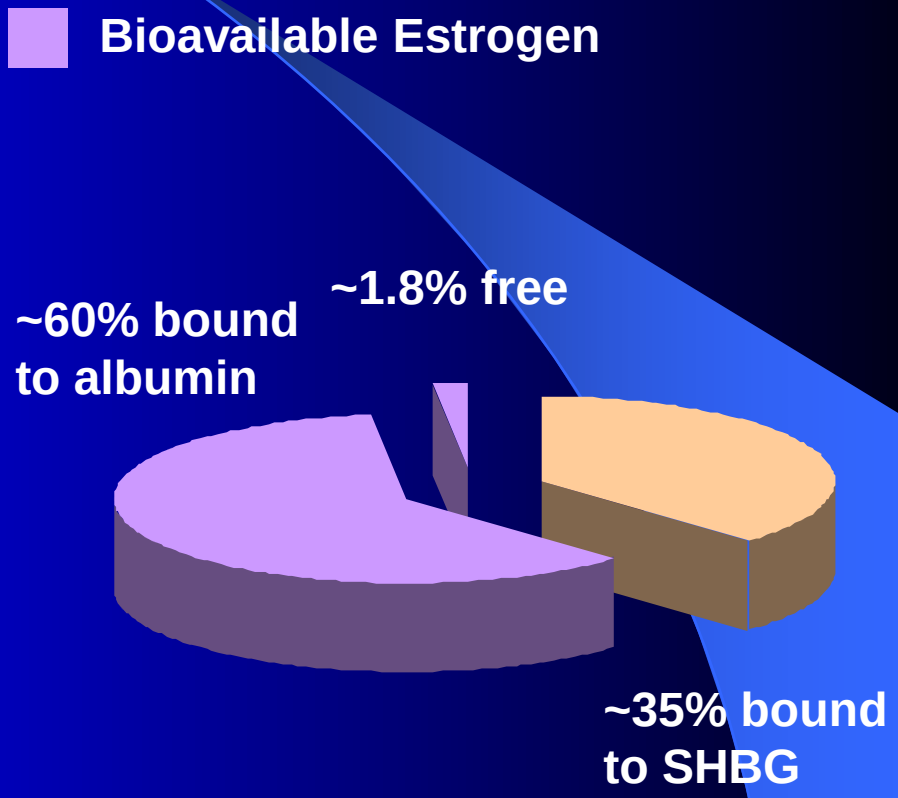


Figure 1 - The steroid testosterone dissocociates from its binding molecule (SHBG) at the target cell. Testosterone then enters the target cell and binds with its receptor. This complex then translocates to the nucleus affecting protein synthesis, causing cellular effects such as growth, spermatogenesis. This "genomic" pathway is responsible for the primary post-pubertal actions of testosterone.

Testosterone and Estrogen Circulation in the Body





Simon JA. *Fert Steril*. 2002;77:S77-S82.
Demers LM. In: Redmond, G, ed. *Androgenic Disorders*. Raven Press, New York, NY; 1995:21-34.

Free T + Albumen-bound T

= Bioavailable T

- Free and bioavailable T generally reflect the clinical situation more accurately than total T
- BioT levels decline more rapidly with age than Total T and FreeT. Bio T best assay for this.

Assays for Free and Bioavailable Testosterone

- Free T by Equilibrium Dialysis is best method but very labour intensive
- Bioavailable T by precipitation of SHBG bound T with ammonium sulphate

Measurement of Androgen Status

- Total Testosterone is widely used
- Early morning test before 0800-1000h
- Total Testosterone has to be low at least 2 separate days
- Total T is a good predictor of hypogonadism
- Measured free T (by equilibrium dialysis) & Bioavailable T are better predictors of hypogonadism in borderline cases.

- There are no generally accepted lower limits of normal testosterone levels
- Normal ranges differ between laboratories
- The most widely quoted range for Total Testosterone is:- 10 – 30 nmol/l

ISA, ISSAM, EAU Recommendations

- Testosterone <8 nmol/l very likely to require TRT
- Testosterone >12 nmol/l do not require TRT
- Testosterone 8-11.9 nmol/l in subjects with symptoms require further evaluation and consideration for trials of TRT

Nieschlag et al J Androl 2006; 27:135-137

Historical overview of testosterone preparations available for clinical use.

1940 1954 1977 1992 1995 1998 2002 2004 2004

Epidemiological Studies in Healthy Men that show low Testosterone Predicts Later-onset of Diabetes

- Mass Male Aging (1156) 7-10yr ↓ FT
- MRFIT (528) 5yr ↓ TT ↓FT
- Rancho-Bernado (294) 8yr ↓ TT
- Tibblin (659) 5yr ↓ TT

Low Levels of Testosterone and SHBG Play a Role in the Development of Insulin Resistance and Subsequent Type 2 Diabetes: Prospective Results from the Massachusetts Male Aging Study

Predictor	Increment	OR*	P
Free testosterone	- 1 SD (3.9 ng/dL)	1.58	0.017
SHBG	- 1 SD (15.8 nmol/L)	1.89	0.014
Hypertension	Presence	2.18	0.018
Heart disease	Presence	1.96	0.11
Depression	Presence	3.09	0.008
BMI	+ 1 SD (4.0 kg/m^2)	1.83	< 0.001

Data are from 1987 to 1989 with a 9-year follow-up.

*OR in favor of incident diabetes

Stellato RK et al. Diabetes Care 23(4): 490-494 (2000)

Testosterone and Sex Hormone–Binding Globulin Predict the Metabolic Syndrome and Diabetes in Middle-Aged Men

DAVID E. LAAKSONEN, MD, PHD, MPH[1,2]
LEO NISKANEN, MD, PHD[1]
KARI PUNNONEN, MD, PHD[3]
KRISTIINA NYYSSÖNEN, PHD[4]
TOMI-PEKKA TUOMAINEN, MD[4]
VELI-PEKKA VALKONEN, MD[4]
RIITTA SALONEN, MD, PHD[4,5]
JUKKA T. SALONEN, MD, PHD, MSCIH[4,5,6]

OBJECTIVE — In men, hypoandrogenism is associated with features of the metabolic syndrome, but the role of sex hormones in the pathogenesis of the metabolic syndrome and diabetes is not well understood. We assessed the association of low levels of testosterone and sex hormone–binding globulin (SHBG) with the development of the metabolic syndrome and diabetes in men.

RESEARCH DESIGN AND METHODS — Concentrations of SHBG and total and calculated free testosterone and factors related to insulin resistance were determined at baseline in 702 middle-aged Finnish men participating in a population-based cohort study. These men had neither diabetes nor the metabolic syndrome.

RESULTS — After 11 years of follow-up, 147 men had developed the metabolic syndrome (National Cholesterol Education Program criteria) and 57 men diabetes. Men with total testosterone, calculated free testosterone, and SHBG levels in the lower fourth had a severalfold increased risk of developing the metabolic syndrome (odds ratio [OR] 2.3, 95% CI 1.5–3.4; 1.7, 1.2–2.5; and 2.8, 1.9–4.1, respectively) and diabetes (2.3, 1.3–4.1; 1.7, 0.9–3.0; and 4.3, 2.4–7.7, respectively) after adjustment for age. Adjustment for potential confounders such as cardiovascular disease, smoking, alcohol intake, and socioeconomic status did not alter the associations. Factors related to insulin resistance attenuated the associations, but they remained significant, except for free testosterone.

CONCLUSIONS — Low total testosterone and SHBG levels independently predict development of the metabolic syndrome and diabetes in middle-aged men. Thus, hypoandrogenism is an early marker for disturbances in insulin and glucose metabolism that may progress to the metabolic syndrome or frank diabetes and may contribute to their pathogenesis.

Diabetes Care 27:1036–1041, 2004

to be an independent relationship between low levels of testosterone and hyperinsulinemia (4) and dyslipidemia (8). Low levels of testosterone have also predicted worsening abdominal obesity (9).

Testosterone itself may have a central or permissive role in the pathogenesis of the metabolic syndrome and type 2 diabetes by increasing skeletal muscle tissue and decreasing abdominal obesity and nonesterified fatty acids, consequently improving insulin sensitivity (10). Overall or abdominal obesity increases glucocorticoid turnover and production, which disturbs regulation of the hypothalamic-pituitary-adrenal axis (11,12) and may contribute to mild hypoandrogenism in men. An imbalance between levels of testosterone and its metabolite dihydrotestosterone could also contribute (13).

Orchiectomized rats show marked insulin resistance, confined to peripheral tissues, and these metabolic abnormalities are corrected by physiological doses of testosterone (14). In relatively small randomized controlled trials, androgen treatment has improved insulin sensitivity in middle-aged abdominally obese men (10,15), although findings have not

0021-972X/06/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 91(3):843–850

doi: 10.1210/jc.2005-1326

Low Sex Hormone-Binding Globulin, Total Testosterone, and Symptomatic Androgen Deficiency Are Associated with Development of the Metabolic Syndrome in Nonobese Men

Varant Kupelian, Stephanie T. Page, Andre B. Araujo, Thomas G. Travison, William J. Bremner, and John B. McKinlay

New England Research Institutes (V.K., A.B.A., T.G.T., J.B.M.), Watertown, Massachusetts 02472; and University of Washington (S.T.P., W.J.B.), Seattle, Washington 98195

Background: The metabolic syndrome (MetS), characterized by central obesity, lipid and insulin dysregulation, and hypertension, is a precursor state for cardiovascular disease. The purpose of this analysis was to determine whether low serum sex hormone levels or clinical androgen deficiency (AD) predict the development of MetS.

Methods: Data were obtained from the Massachusetts Male Aging Study, a population-based prospective cohort of 1709 men observed at three time points (T_1, 1987–1989; T_2, 1995–1997; T_3, 2002–2004). MetS was defined using a modification of the ATP III guidelines. Clinical AD was defined using a combination of testosterone levels and clinical signs and symptoms. The association between MetS and sex hormone levels or clinical AD was assessed using relative risks (RR), and 95% confidence intervals (95% CI) were estimated using Poisson regression models.

Results: Analysis was conducted in 950 men without MetS at T_1. Lower levels of total testosterone and SHBG were predictive of MetS, particularly among men with a body mass index (BMI) below 25 kg/m^2 with adjusted RRs for a decrease in 1 SD of 1.41 (95% CI, 1.06–1.87) and 1.65 (95% CI, 1.12–2.42). Results were similar for the AD and MetS association, with RRs of 2.51 (95% CI, 1.12–5.65) among men with a BMI less than 25 compared with an RR of 1.22 (95% CI, 0.66–2.24) in men with a BMI of 25 or greater.

Conclusions: Low serum SHBG, low total testosterone, and clinical AD are associated with increased risk of developing MetS over time, particularly in nonoverweight, middle-aged men (BMI, <25). Together, these results suggest that low SHBG and/or AD may provide early warning signs for cardiovascular risk and an opportunity for early intervention in nonobese men. (*J Clin Endocrinol Metab* 91: 843–850, 2006)

Epidemiological Studies of Testosterone Levels in men with Type 2 Diabetes

Study	Diabetic	Healthy	Outcome
Ando 1984	41	47	↓ TT
Barrett-Connor 1990	110	875	↓ TT
Barrett-Connor 1992	44	88	↓TT, BioT
Zietz 2000	155	155	↓FT
Anderson 1994	46	11	↓TT
Dhindsa 2004	103	-	↓FT

Hypogonadism and Diabetes Dhindsa et al. New York State University JCEM Nov 2004

- 33% of men with Type 2 Diabetes found to be hypogonadal based on measurement of free T measured by Equilibrium Dialysis

Testosterone Levels in Men with Type 2 Diabetes

- 355 men studied from Urban population of Barnsley recruited from Diabetic Retinopathy Screening Clinic

Treatments

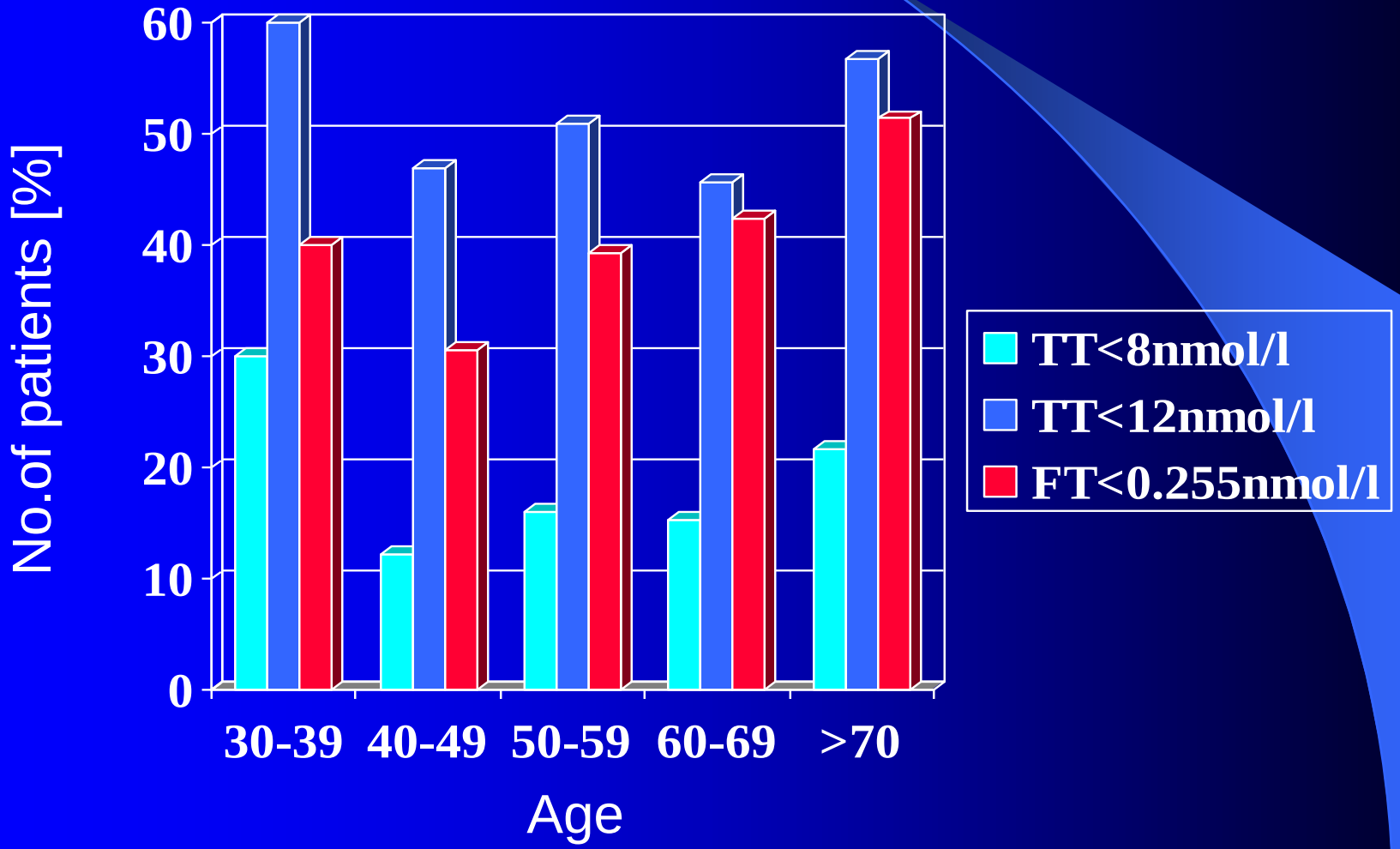
Diet alone	70	70
Metformin	62	
Gliclazide	32	
Metformin + Gliclazide	75	
Metformin + TZD	11	190
Metformin + Acarbose	3	
Gliclazide + TZD	5	
Metformin + Gliclazide + TZD	2	
Insulin + Metformin	40	95
Insulin	55	

Parameter	Mean ± SEM	Sample range
Age (years)	58.05 ± 0.54	32 - 83
HbA1c (%)	7.22 ± 0.07	4.1 – 13.3
Total Testosterone (nmol/L)	12.72 ± 0.29	2.6 – 39
SHBG (nmol/L)	32.48 ± 1.06	5.14 – 129
Bioavailable testosterone (nmol/L)	4.03 ± 0.08	0.89 – 11.49
Calculated bioavailable testosterone (nmol/L)	4.01 ± 0.08	0.97 – 11.73
Calculated free testosterone (nmol/L)	0.274 ± 0.01	0.05 – 1.02
FSH (u/L)[1]	9.66 ± 0.87	2.3 – 58.1
LH (u/L)[1]	5.92 ± 0.46	1.1 – 24.7
BMI	32.32 ± 0.31	21.05 – 63.05
Waist circumference (cm)	109.7 ± 0.77	81 - 173
Systolic blood pressure (mm Hg)	143.3 ± 1.01	94 - 200
Diastolic blood pressure (mm Hg)	82.06 ± 0.57	55 - 180

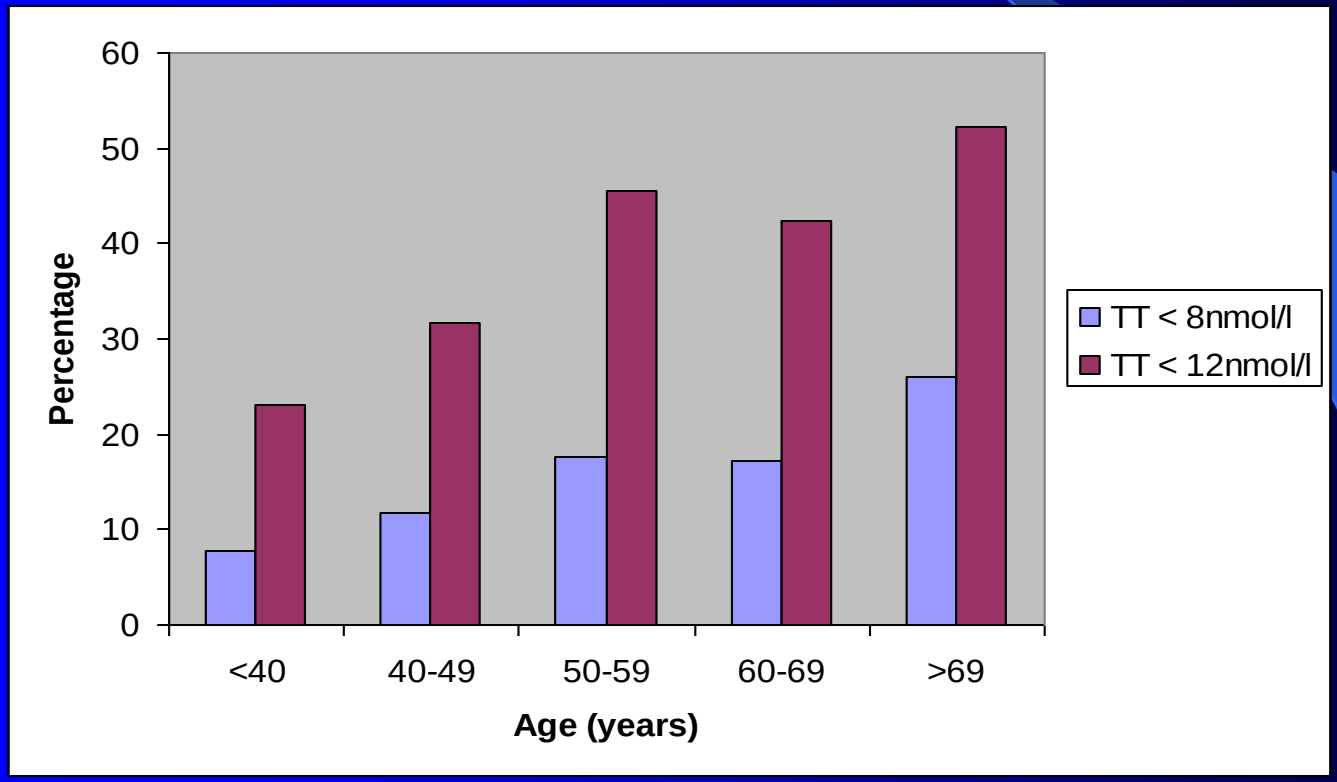
Low Testosterone Levels associated with Symptoms of Hypogonadism

Total T	< 8 nmol/l	17.18%
Total T	< 12 nmol/l	42.25%
Bio T	< 2.5 nmol/l	14.37%
Bio T	< 4.0 nmol/l	43.6%
Calc FT	< 0.255 nmol/l	41.9%

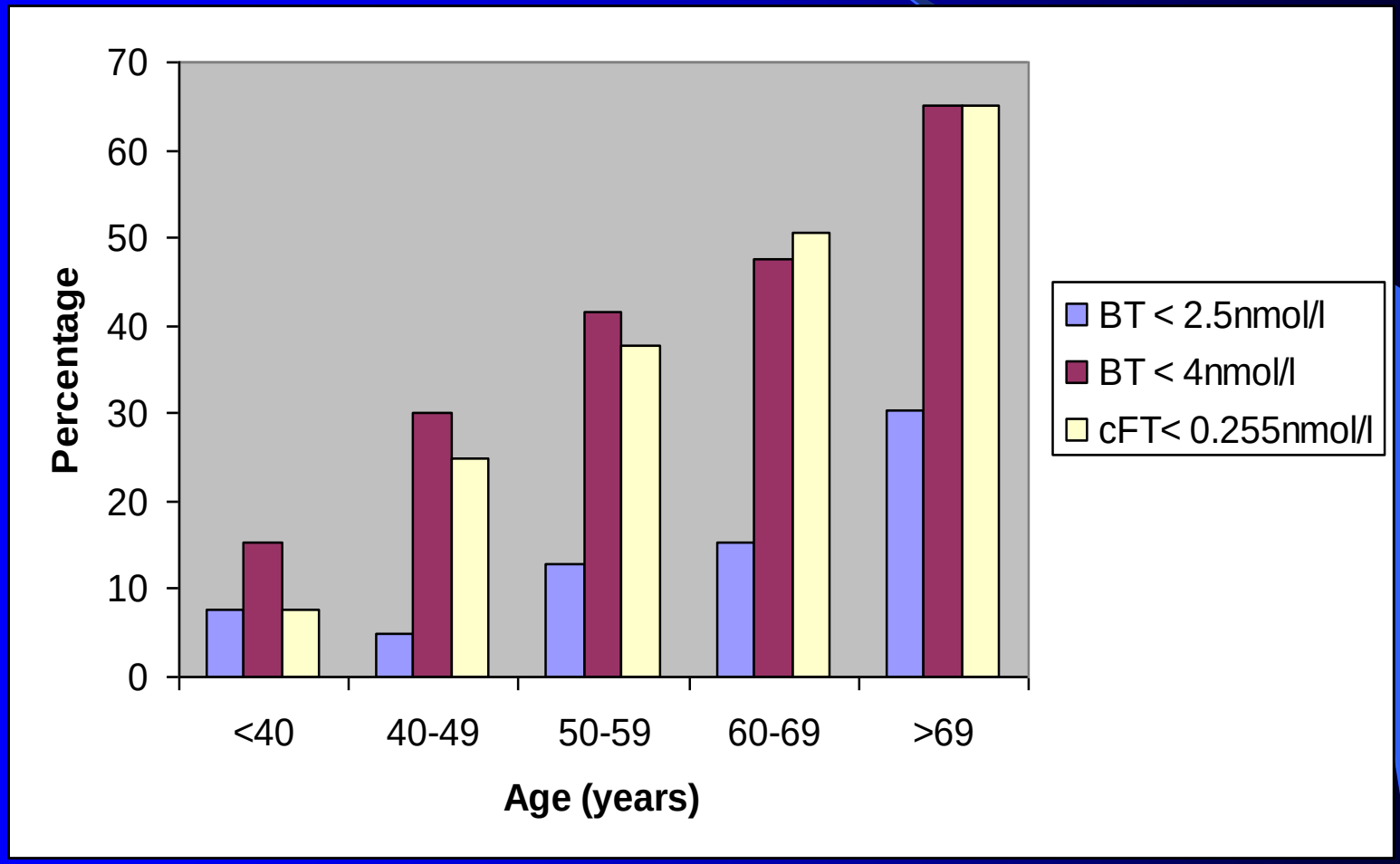
Low Testosterone Levels in Type 2 Diabetes



Hypogonadal Symptoms with Low Total Testosterone



Hypogonadal Symptoms with Low Bioactive Testosterone



Causes of Hypogonadism

- Primary Hypogonadism 26%
- Secondary Hypogonadism 10%
- Mixed Hypogonadism 64%

30 Cross-Sectional Studies of Androgen Levels in CVD

1 reported ↑ T
11 reported ↔
18 reported ↓ T

Table 2
Cross-sectional studies

First author and year	Study size	Androgen	End point	Androgen level in cases
Mendoza, 1983 [23]	52	T	MI	↓
Barth, 1983 [24]	20	T	CAD	↓
Hromadova, 1985 [25]	67	T	C.F.	↓
Breier, 1985 [26]	139	T	CAD	↓
Aksut, 1986 [27]	54	T	MI, AP	↓
Sewdarsen, 1986 [28]	56	T, free T	MI	↓
Chute, 1987 [29]	146	T, free T, ASD	CAD	↓
Hämäläinen, 1987 [30]	57	T, free T, DT	CHD	↓
Lichtenstein, 1987 [31]	2512	T	IHD	↓[a]
Swartz, 1987 [32]	71	T	MI	↓
Sewdarsen, 1988 [33]	20	T	MI	↓
Slowinska-Srzednicka, 1989 [34]	108	T, DT, ASD, DHEAS	MI	↓
Sewdarsen, 1990 [35]	224	T, free T	MI	↓
Herrington, 1990 [36]	103	DHEA, DHEAS	CAD	↓
Gray, 1991 [37]	1709[b]	T, free T, DHEAS, DHEA, ASD	CHD	↓
Rice, 1993 [38]	272[c]	T, free T	MI	↓
Mitchell, 1994 [39]	98	DHEAS, T, free T	MI	↓[d]
Phillips, 1994 [8]	55	T, free T, DHEAS	CAD	↓
Luria, 1982 [40]	50	T	MI	↔
Labropoulos, 1982 [41]	144	T	MI	↔
Phillips, 1983 [42]	122	T	CHD	↔
Heller, 1983 [43]	295	T	CHD	↔
Small, 1985 [44]	100	T	IHD	↔
Franzen, 1986 [45]	92	T	MI	↔
Baumann, 1988 [46]	58	T	'Atherosel.'	↔
Cengiz, 1991 [47]	55	T	MI, AP	↔
Hauner, 1991 [48]	274	T, DHEA, DHEAS	CAD	↔
Hautanen, 1994 [49]	159	T, DHEAS	'C.E.P.'	↔[e]
Marques-Vidal, 1995 [50]	116	T	MI	↔
Zumoff, 1982 [51]	117	T, DT, ASD, DHEA, DHEAS	MI, CAD	↑[f]

Atherosclerosis 1996; 125: 1-13

Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms

K. M. English[1], O. Mandour[2], R. P. Steeds[1], M. J. Diver[3], T. H. Jones[2] and K. S. Channer[1]

[1]*Department of Cardiology, Royal Hallamshire Hospital, Sheffield;* [2]*Department of Human Metabolism and Clinical Biochemistry, University of Sheffield, Sheffield;* [3]*Department of Clinical Chemistry, Royal Liverpool University Hospital, Liverpool, U.K.*

Aims High androgen levels are presumed by many to explain the male predisposition to coronary artery disease. However, natural androgens inhibit male atherosclerosis[1]. Our aim was to determine whether levels of androgens differ between men with and without coronary artery disease.

Methods and Results Ninety male subjects (60 with positive, and 30 with negative coronary angiograms) were recruited. Early morning, fasting blood samples were taken from each patient and free, total and bioavailable testosterone, sex hormone binding globulin, oestradiol, and lipids were measured. Bioavailable testosterone was assayed using a modified technique. Free androgen index was calculated. Men with coronary artery disease had significantly lower levels of free testosterone (mean (standard deviation)); 47·95 (13·77) *vs* 59·87 (26·05) pmol . l^{-1}, P=0·027), bioavailable testosterone; 2·55 (0·77) vs 3·26 (1·18) nmol . l^{-1}, P=0·005 and free androgen index; 37·8 (10·4) vs 48·47 (18·3), P=0·005, than controls. After controlling for differences in age and body mass index the differences in free androgen index and bioavailable testosterone remained statistically significant (P=0·008 and P=0·013, respectively).

Conclusion Men with coronary artery disease have significantly lower levels of androgens than normal controls, challenging the preconception that physiologically high levels of androgens in men account for their increased relative risk for coronary artery disease.

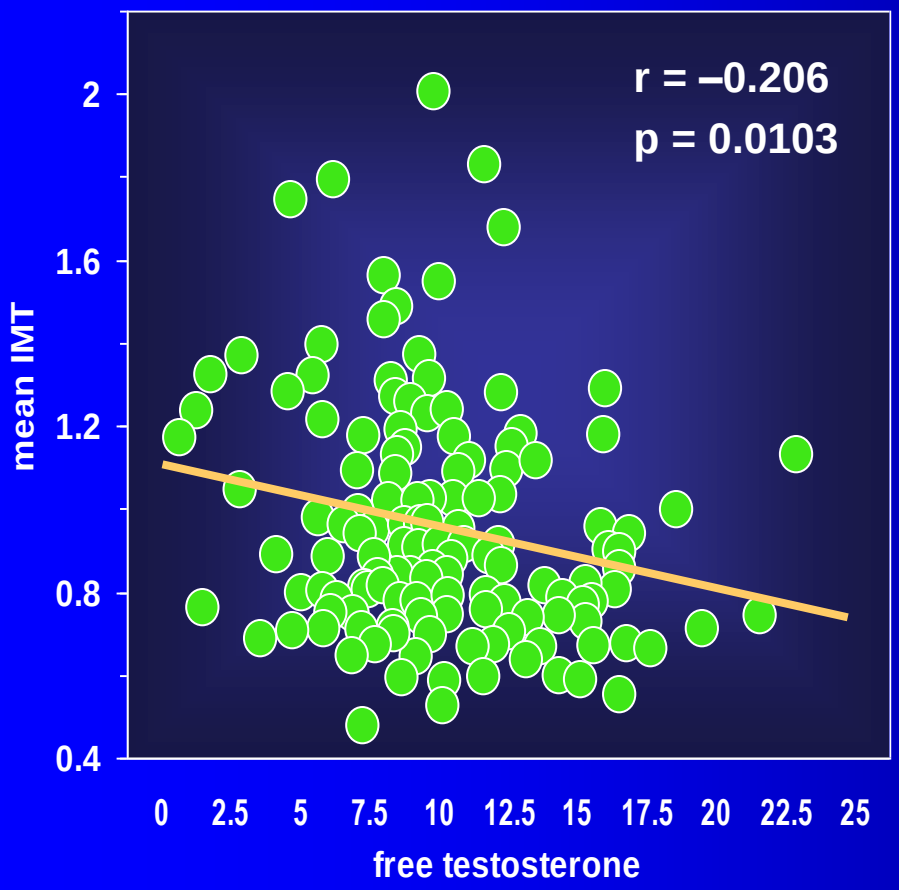
(Eur Heart J 2000; 21: 890–894)

Key Words: Androgens, gender, coronary artery disease, sex hormones.

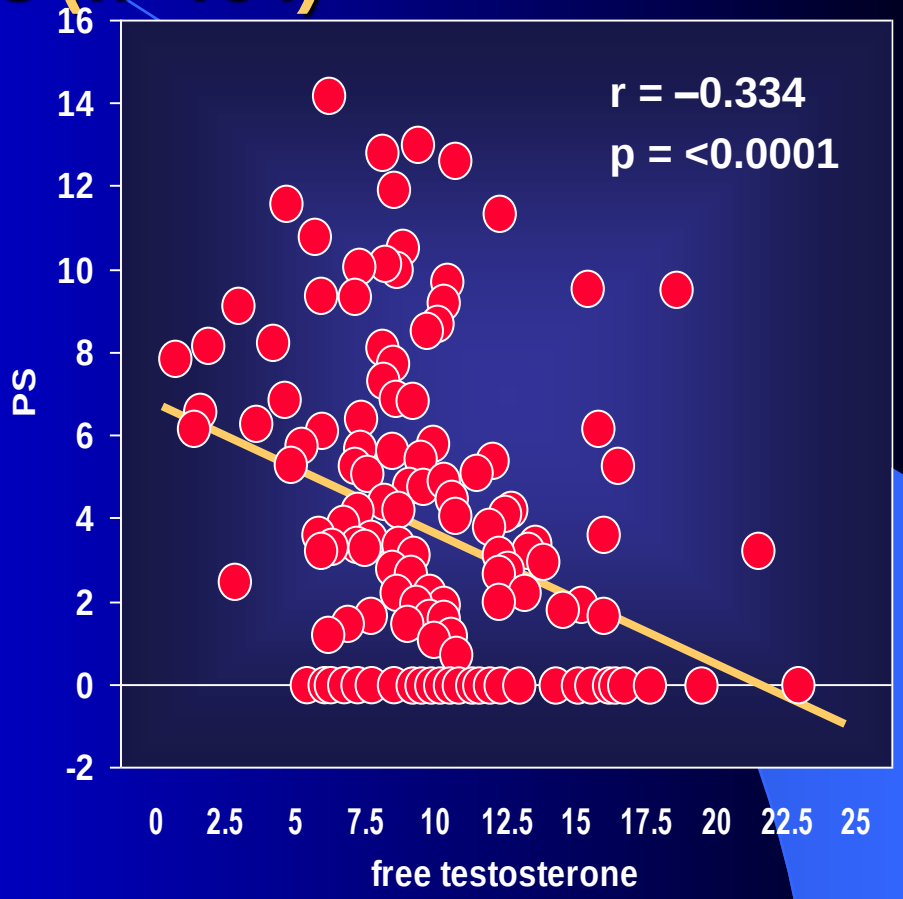
See page 868 for the Editorial comment on this article

European Heart Journal 2000; 21: 890-894

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



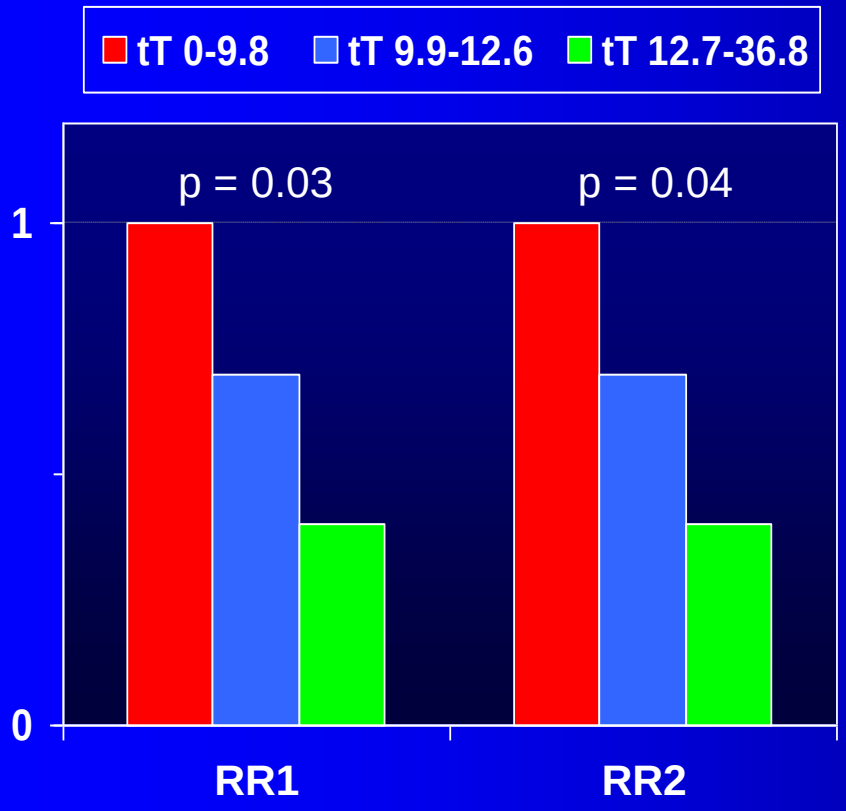
IMT: intima media thickness

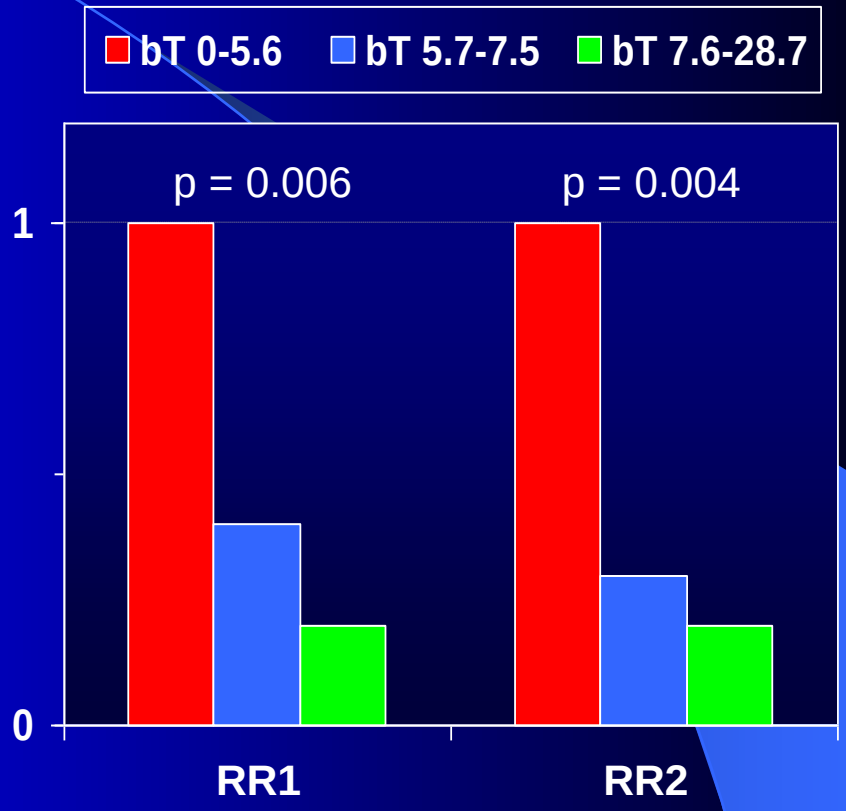


PS: plaque score

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

Low Levels of Testosterone Increase the Risk of Atherosclerosis in 504 Elderly Men: The Rotterdam Study

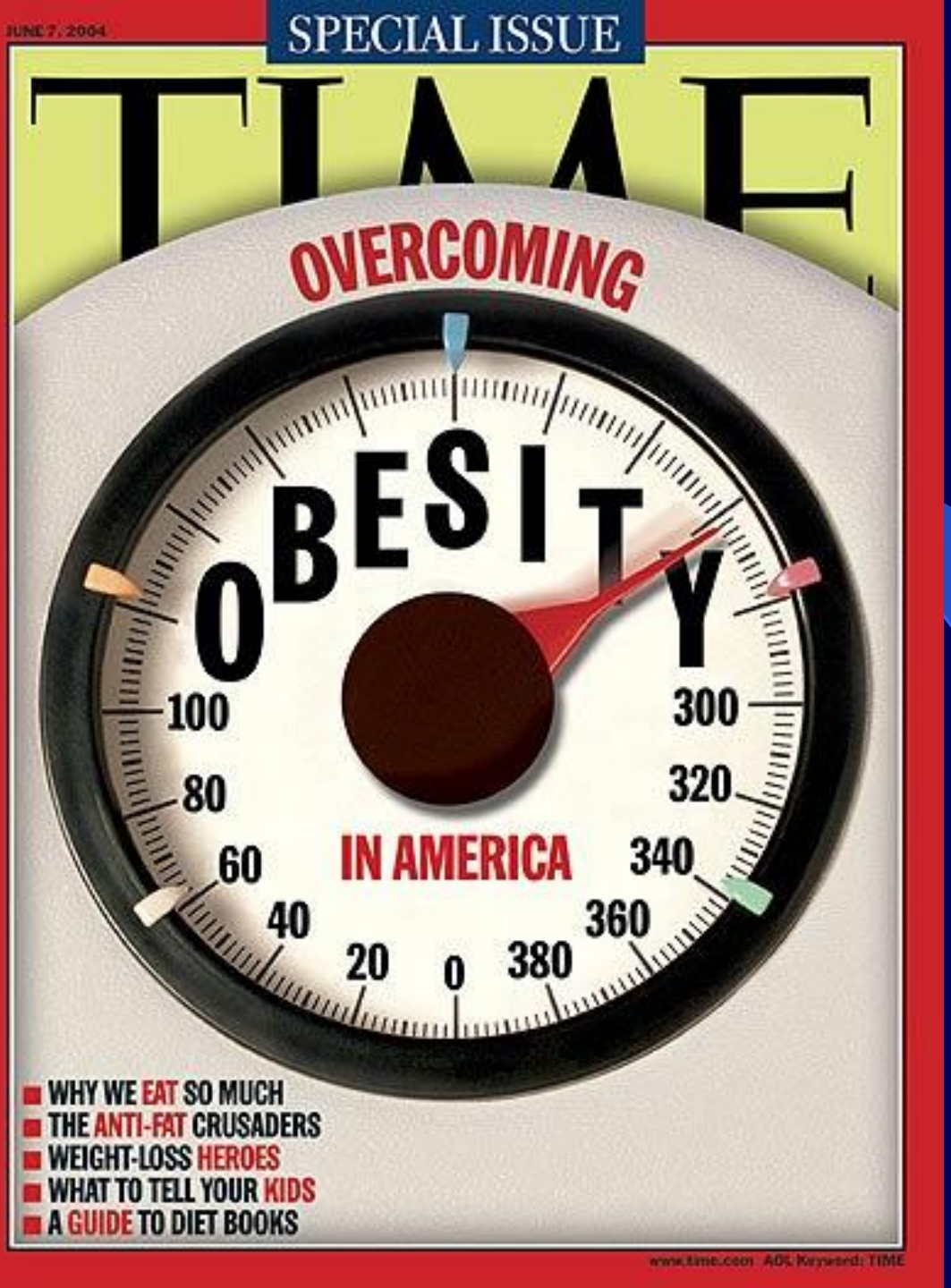




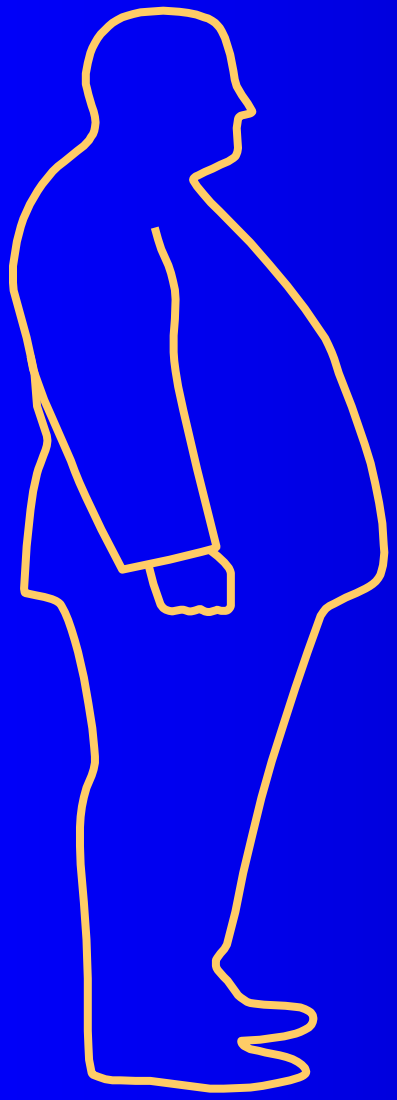
RR1 = Relative Risk for severe aortic atherosclerosis adjusted for age

RR2 = Relative Risk for severe aortic atherosclerosis adjusted for age BMI, SBP, TC, HDL-C, DM (yes/no), smoking (ever/never), and alcohol intake (4 cat.)

Hak AE et al. J Clin Endocrinol Metab 87(8): 3632-3639 (2002)


JUNE 7, 2004
SPECIAL ISSUE
TIME
OVERCOMING
OBESITY
IN AMERICA
100
80
60
40
20
0
300
320
340
360
380
WHY WE EAT SO MUCH
THE ANTI-FAT CRUSADERS
WEIGHT-LOSS HEROES
WHAT TO TELL YOUR KIDS
A GUIDE TO DIET BOOKS
www.time.com AOL Keyword: TIME

Visceral obesity in Type 2 diabetes

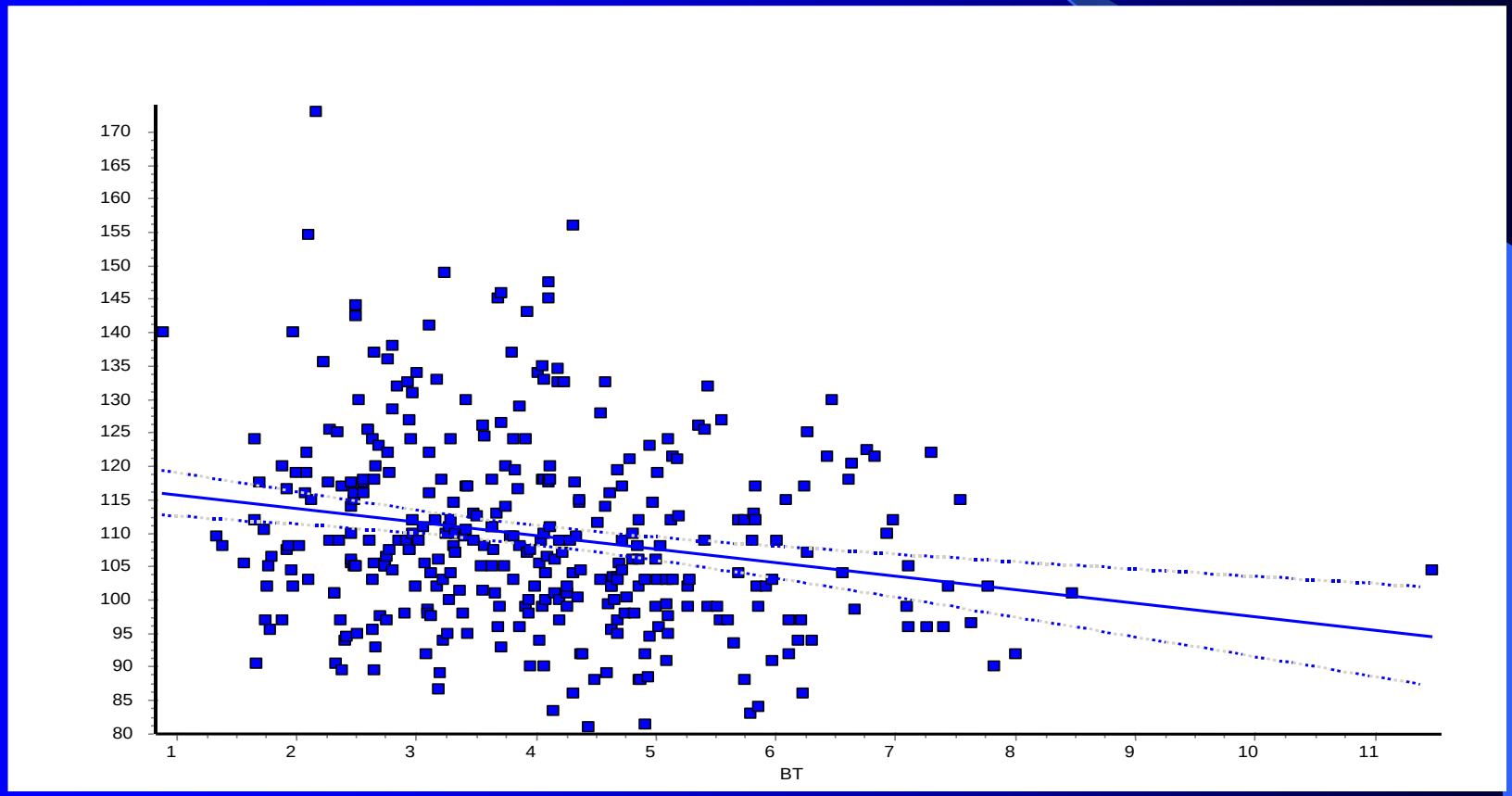


- A major risk factor for CHD[1]
- Associated with insulin resistance[2]

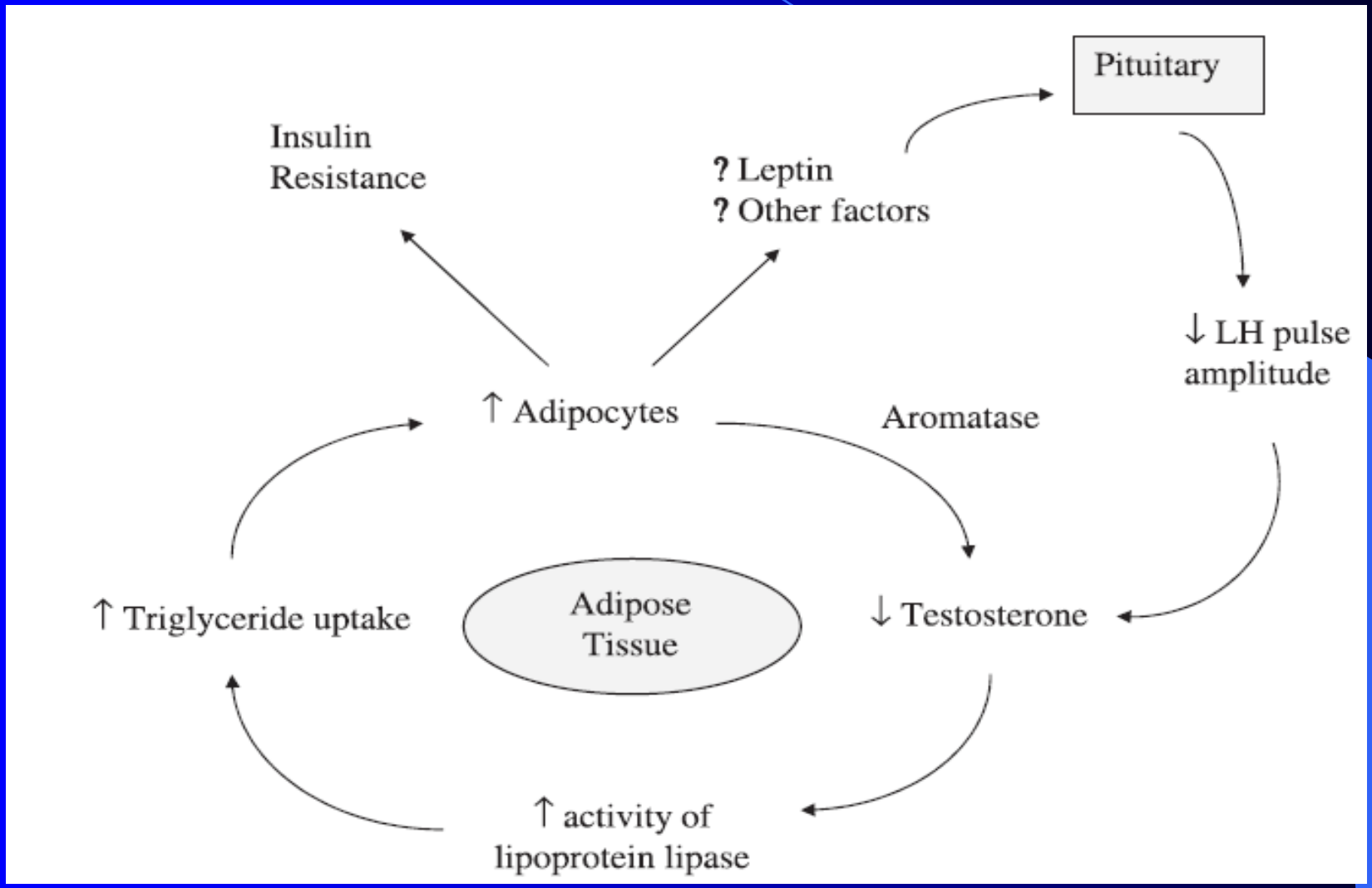
1. Alexander JK. *Am J Med Sci* 2001; 321: 215–224.
2. Bjorntorp P, Rosmond R. *Drugs* 1999; 58 (Suppl 1): 13–18.

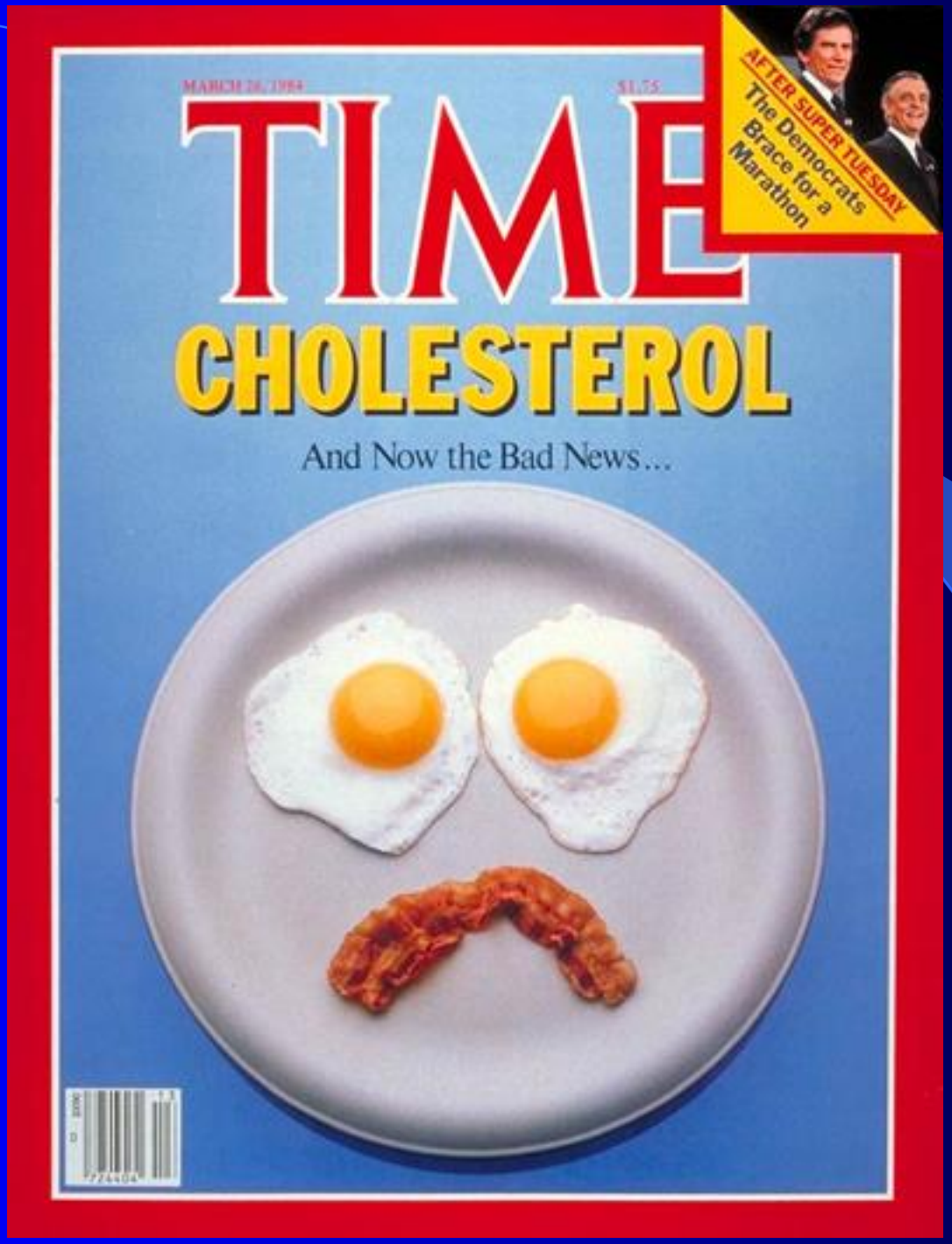
Correlation between Bioavailable Testosterone and Waist Circumference

r= -0.21 p<0.001

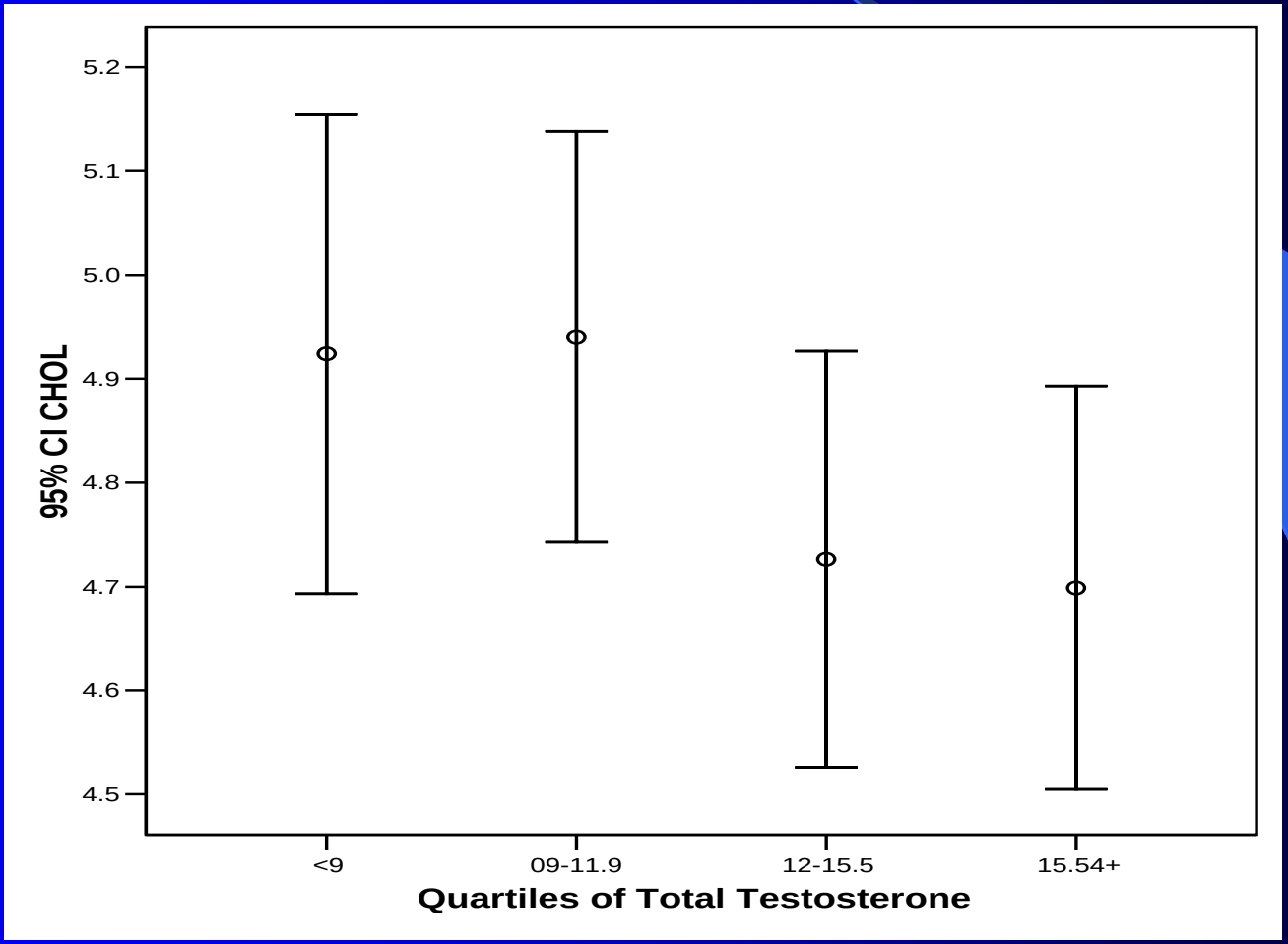


Hypogonadal-Visceral Obesity Cycle

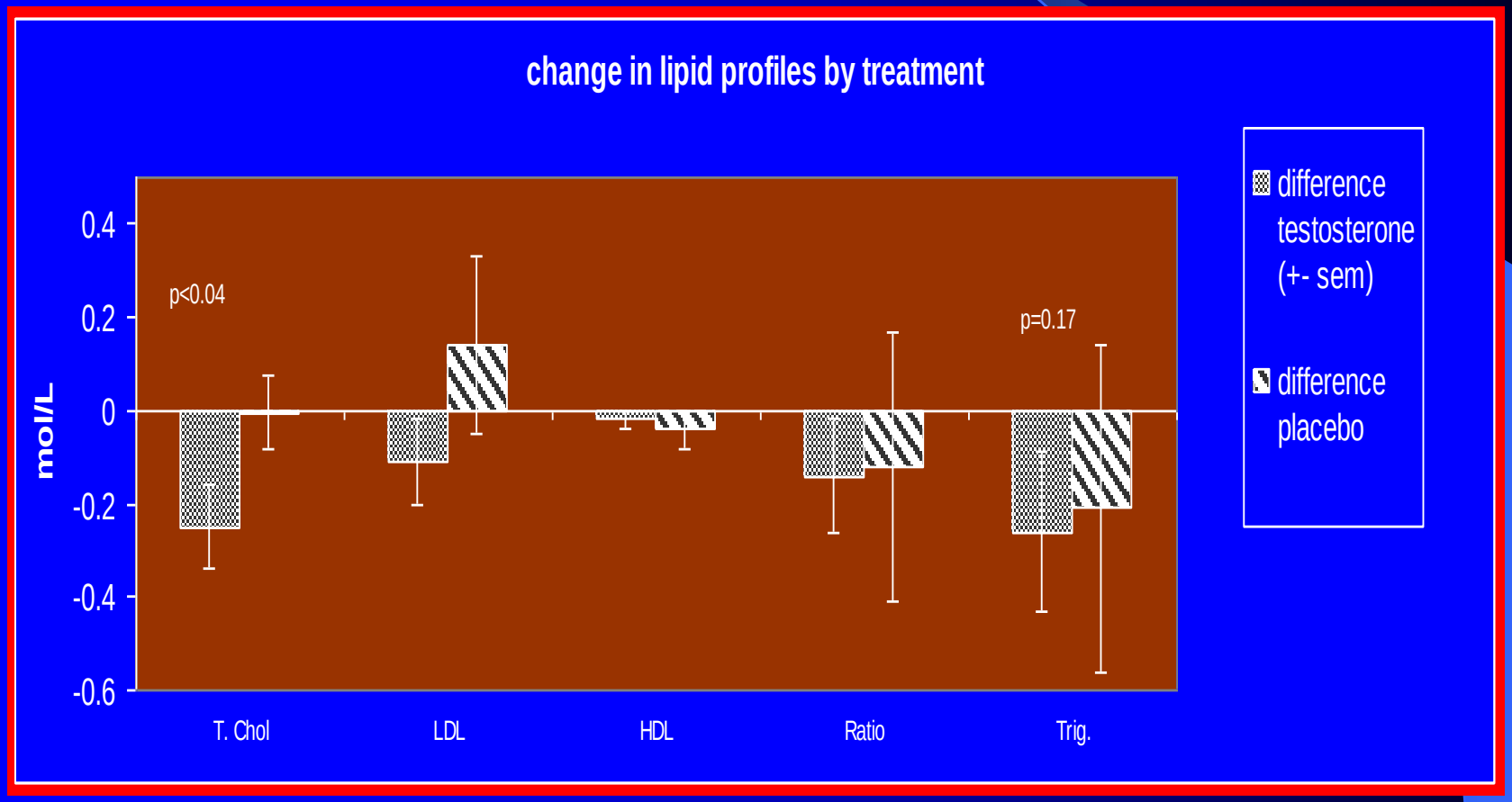



MARCH 26, 1984
$1.75
TIME
CHOLESTEROL
And Now the Bad News...
AFTER SUPER TUESDAY
The Democrats Brace for a Marathon

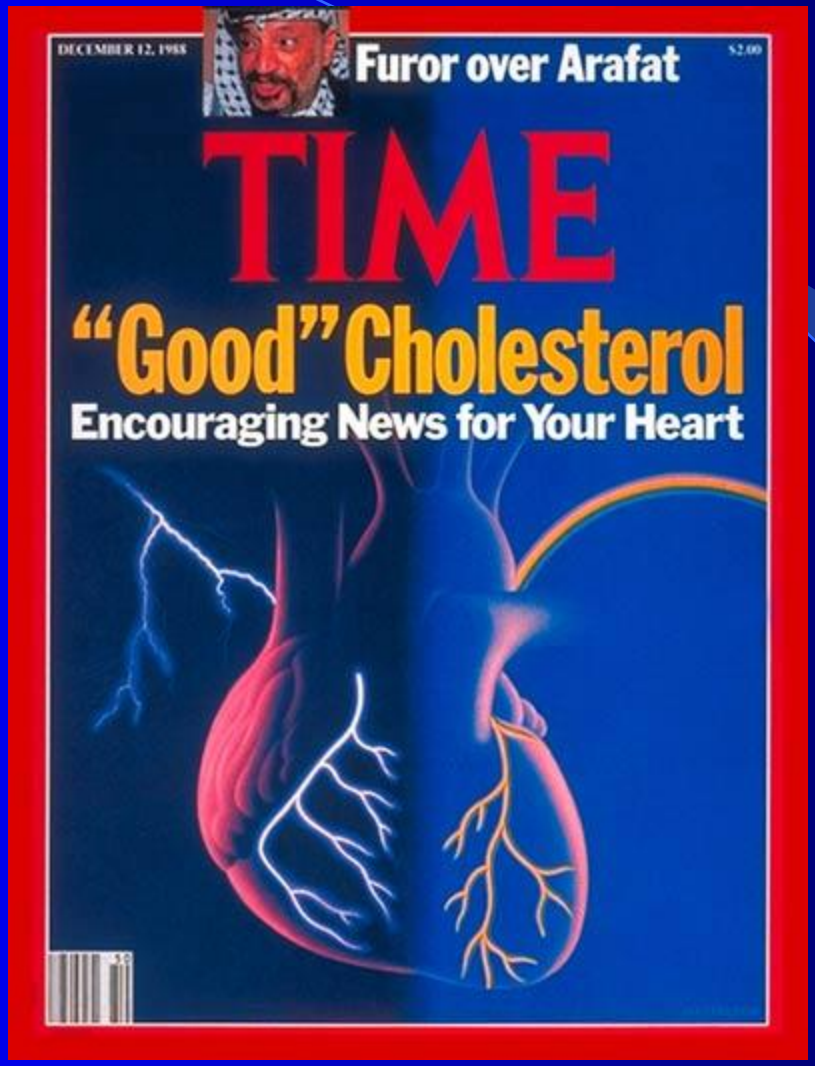
Cholesterol versus Total T in Diabetic Men



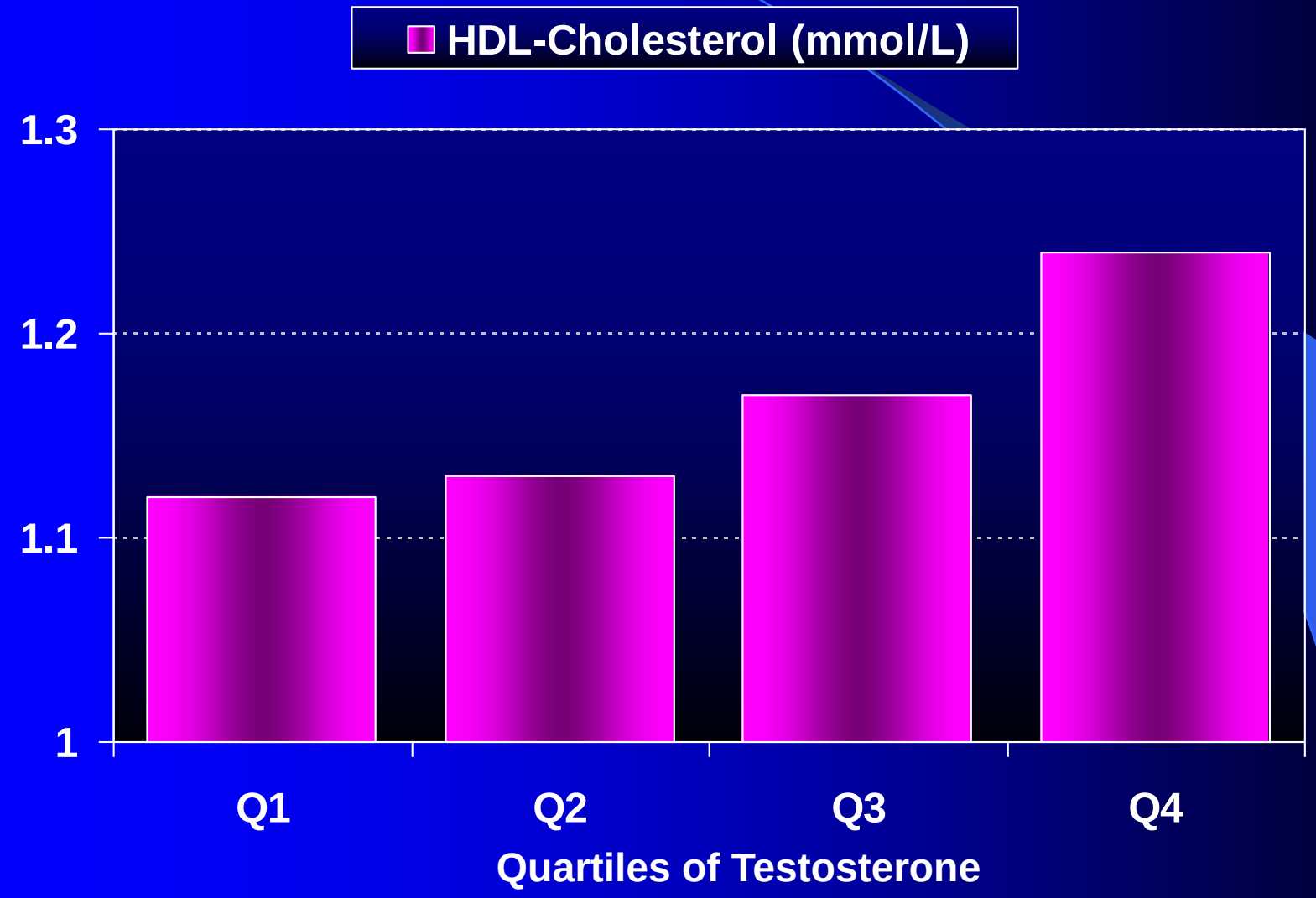
Effect of Testosterone Replacement on Lipid Profiles in Hypogonadal Men with Coronary Heart Disease on Statins



Malkin CJ etal., JCEM 2004: 89;3313-18

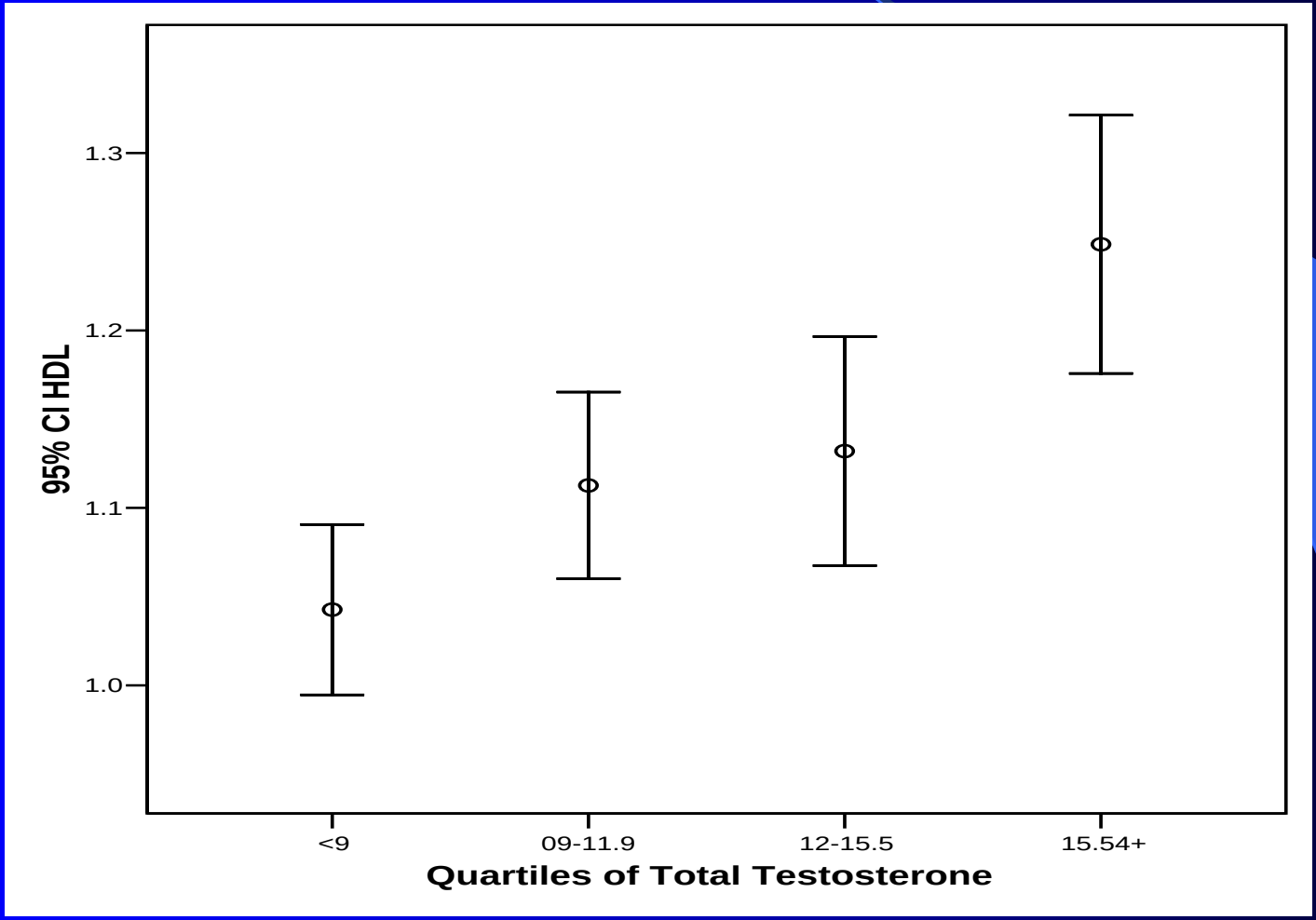

DECEMBER 12, 1988
$2.00
Furor over Arafat
TIME
"Good" Cholesterol
Encouraging News for Your Heart

Testosterone Is the Most Important Independent Hormonal Determinant of HDL-Cholesterol Levels in 715 Healthy Men



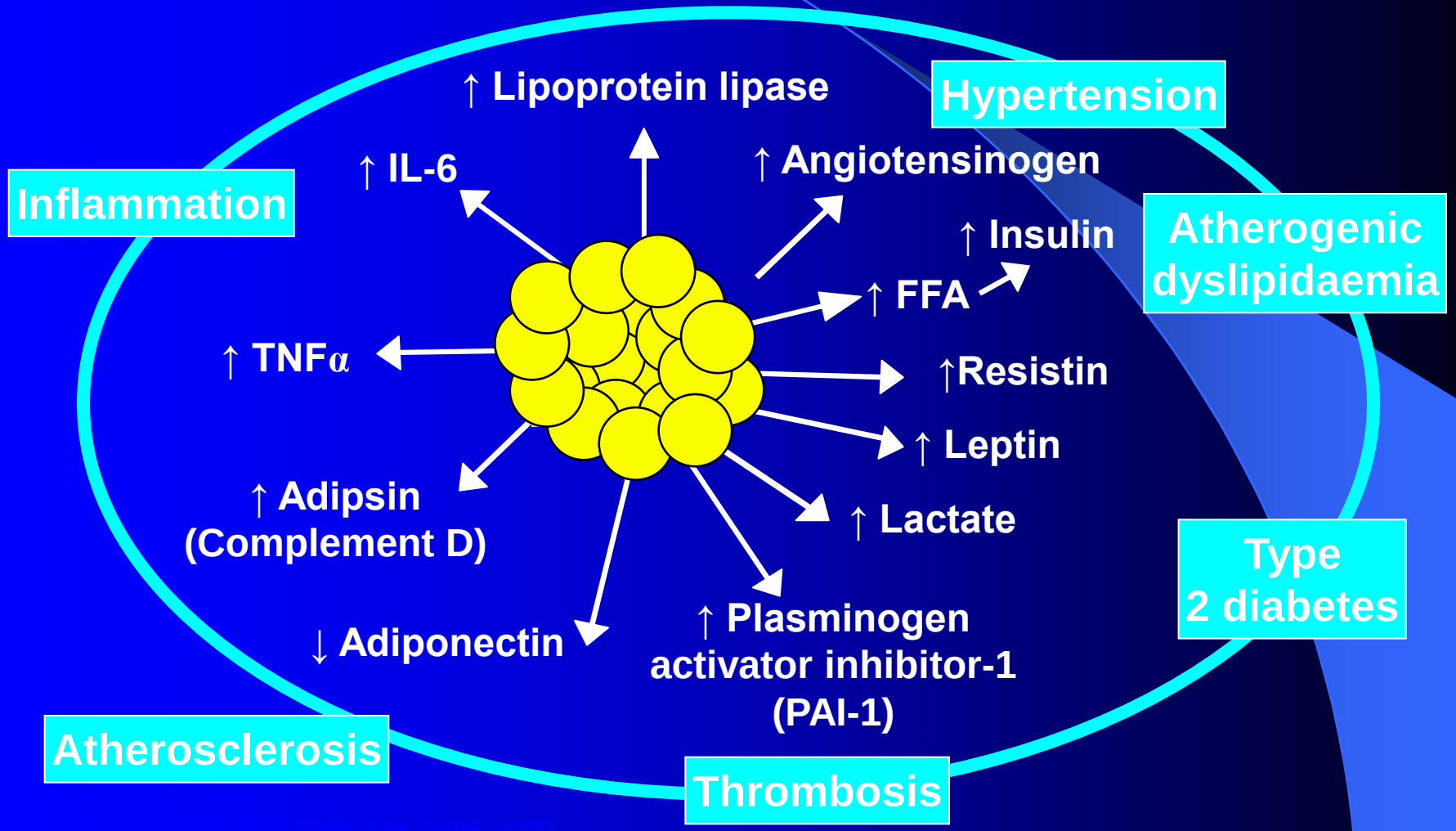
Van Pottelbergh I et al. Atherosclerosis 166: 95-102 (2003)

HDL levels versus Total T in Diabetic men

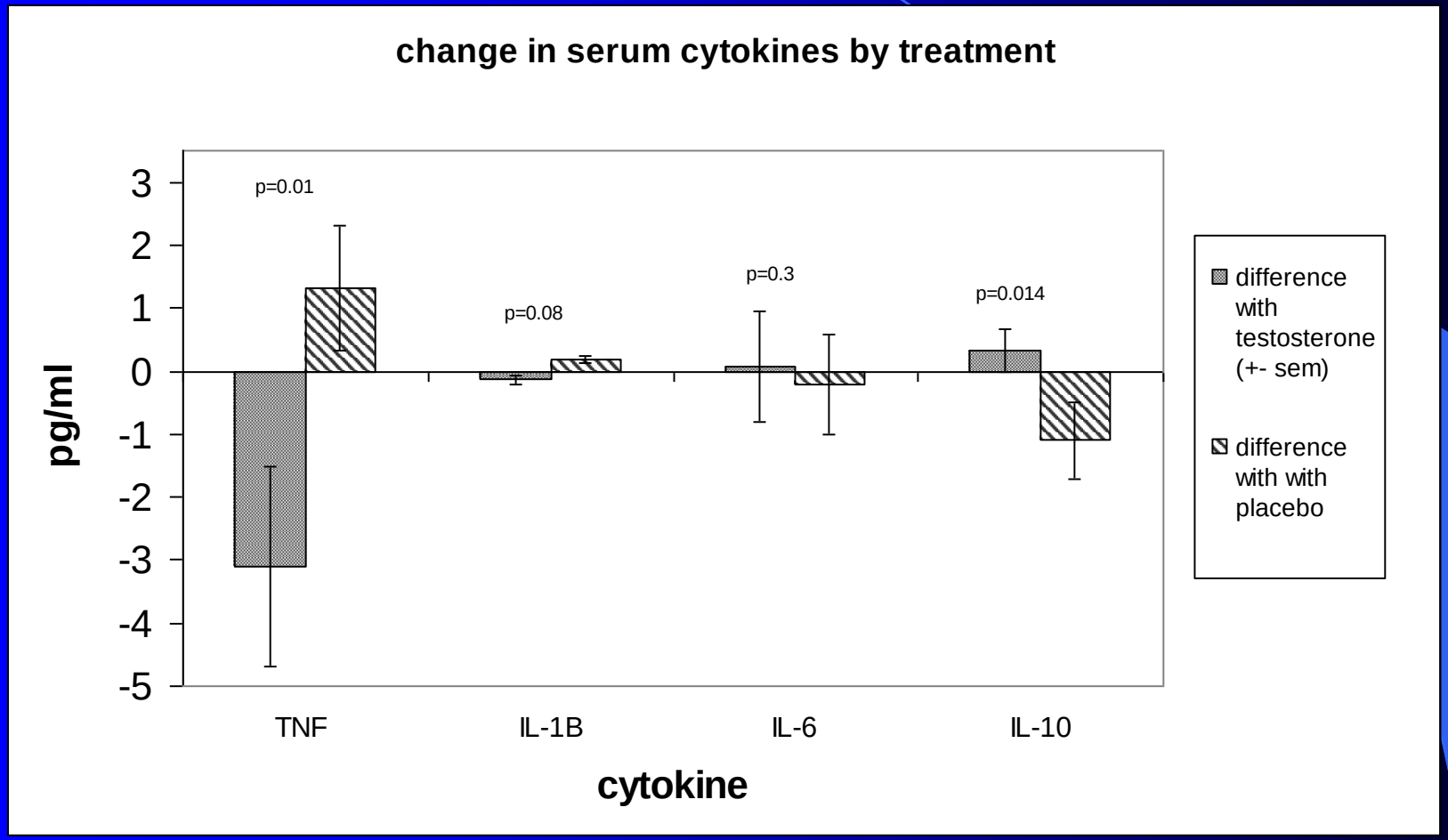



FEBRUARY 23, 2004
TIME
BUSH'S MILITARY RECORDS
IS DISNEY MOUSETRAPPED?
THE SECRET KILLER
The surprising link between INFLAMMATION and HEART ATTACKS, CANCER, ALZHEIMER'S and other diseases
What you can do to fight it

Visceral fat is an active endocrine organ



Effect of TRT on Serum Cytokine Levels in Men with Hypogonadism



Malkin CJ et al., JCEM 2004: 89; 3313-18

Summary

- Significant number of men with type 2 Diabetes who have symptomatic hypogonadism
- 36% have classical hypogonadism
- Testosterone levels correlate strongly with visceral obesity
- Are there any benefits from treating these men?

Potentially Modifiable Cardiovascular Risk Factors by Testosterone

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

Interventional Studies of TRT in Type 2 Diabetes

- Boyanov et al 2003 Non-blinded study 48 men half given oral T half placebo. Reduction in HbA1c (10.4 to 8.6%), BMI
- Corrales et al 2004 No effect in 10 men
- No studies on insulin resistance

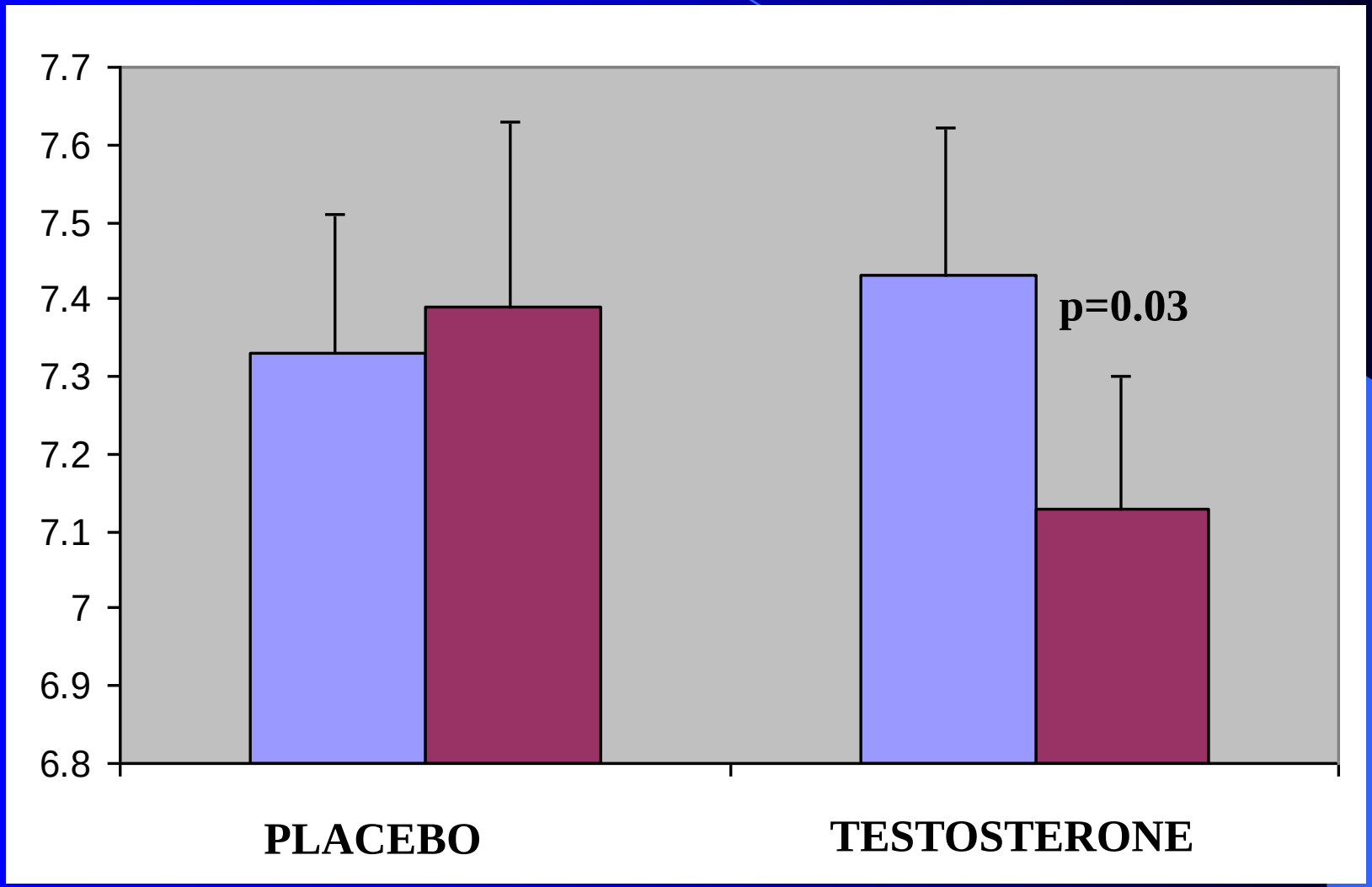
Double-blind Placebo Crossover Study to investigate the effect of TRT on Insulin resistance and Glycaemic control in Hypogonadal Men with Type 2 Diabetes

- 24 men with Type 2 Diabetes (3 diet, 11 oral, 10 insulin)
- Treated for 3 months with Sustanon 200mg/fortnight with 1 month washout between crossover
- Mean Age 64yrs (range 52-76)
- BMI 33 (26.4-45)
- Waist Circumference 115.1 (97.5-141)
- HbA1c 7.2% (5.8-9.4)
- Mean Total Testosterone 8.63nmol/l (2.34-11.62)
- Mean SHBG 27.4nmol/l (11.7-63.4)
- Mean Bioavailable Testosterone 2.73nmol/l (0.6-4.0)

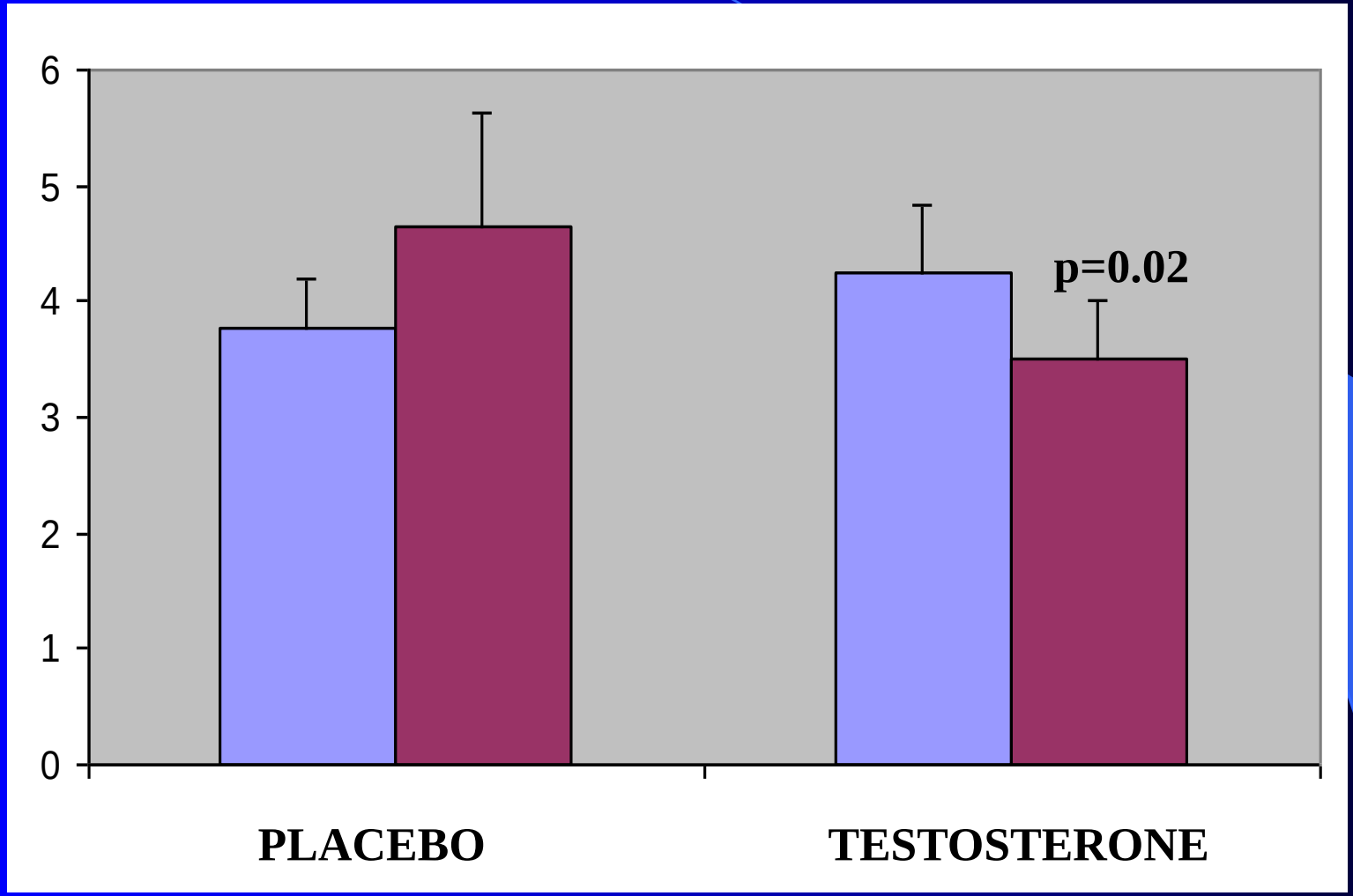
Measurements

- HOMA-IR (3 samples 5 minutes apart for fasting insulin and glucose
- HOMA = mean fI x mean fG / 22.5
- HbA1c
- Lipids
- Waist circumference, waist hip ratio, BMI, % body fat

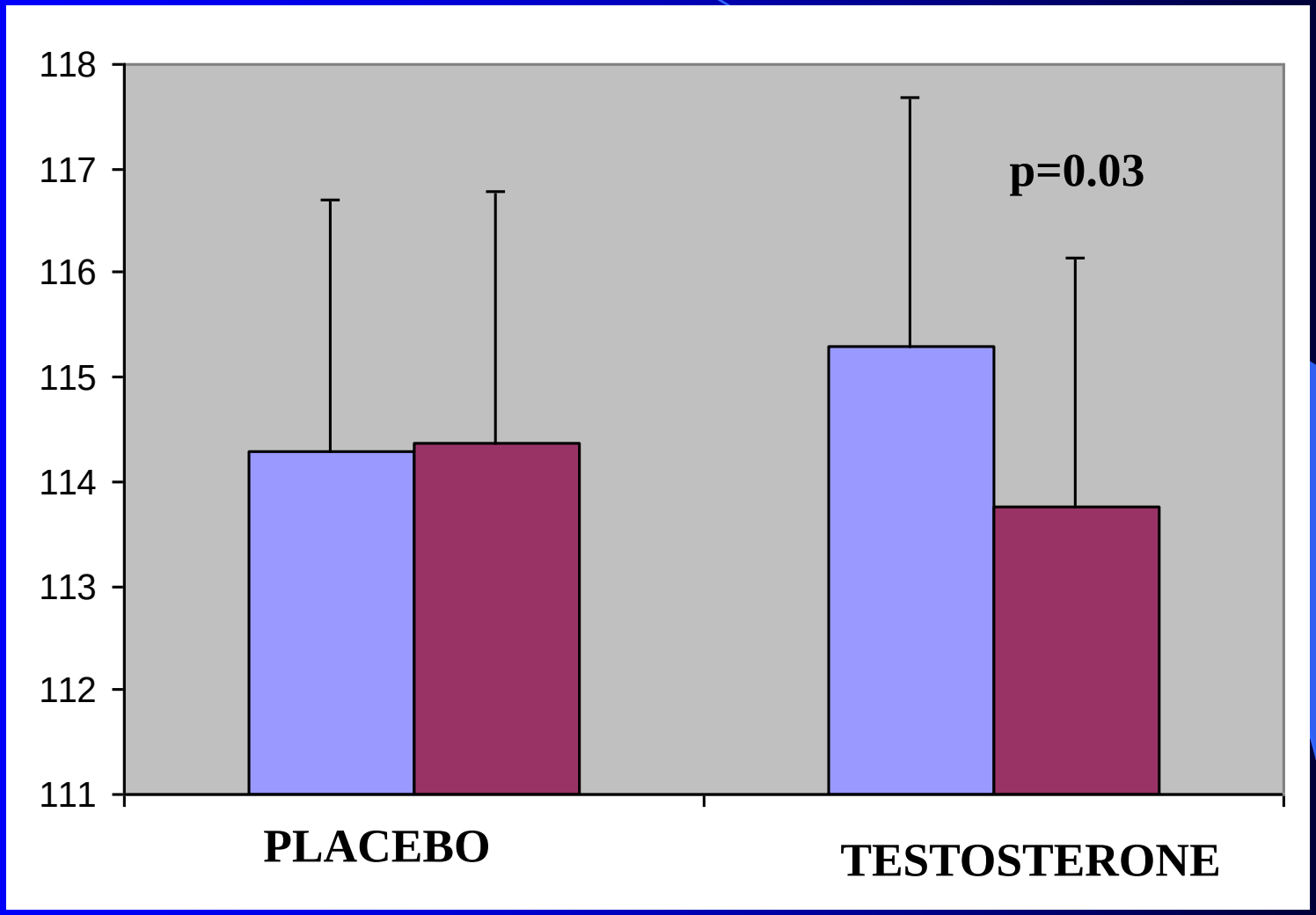
HbA1c



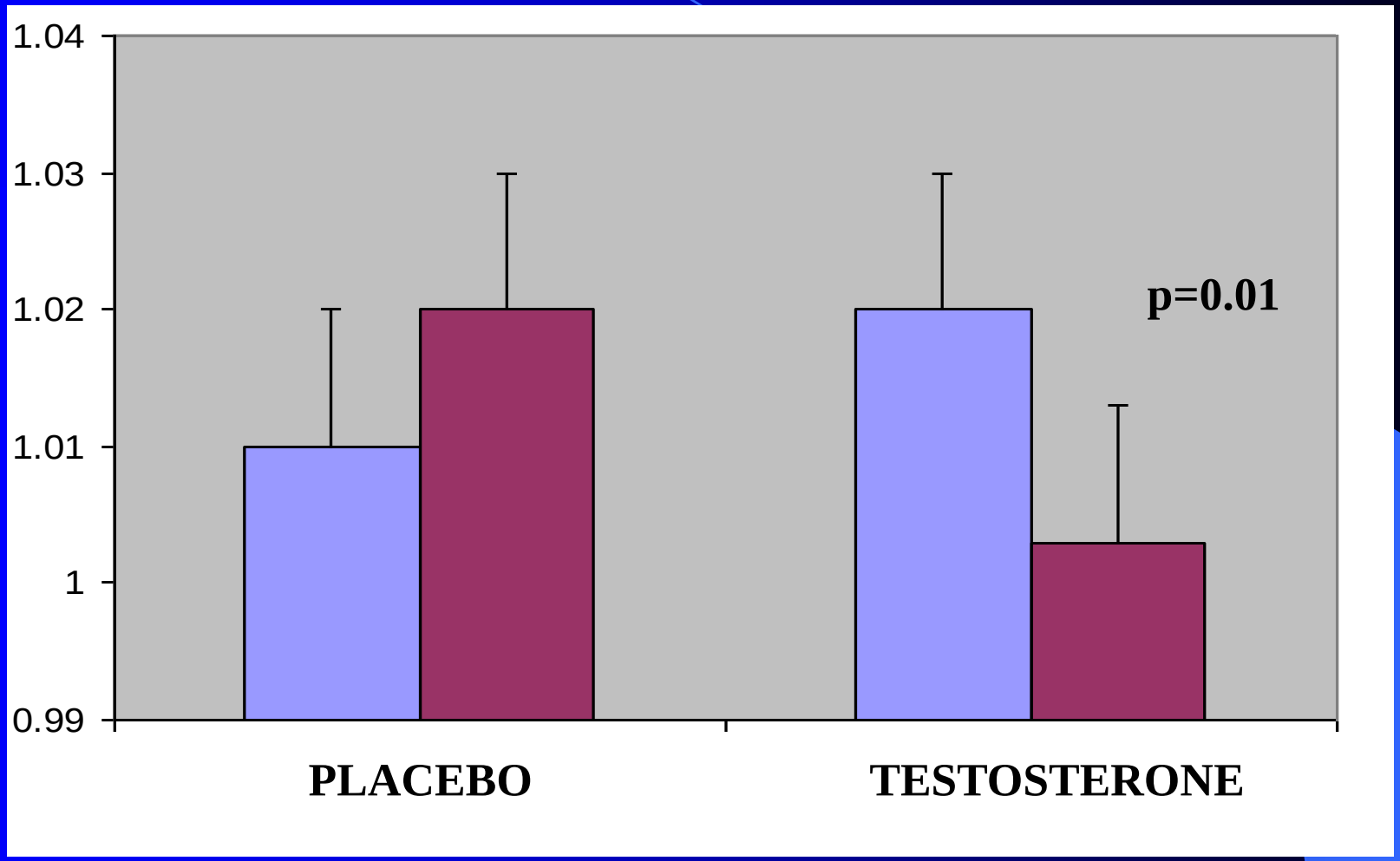
HOMA-IR



Waist circumference



Waist / Hip ratio

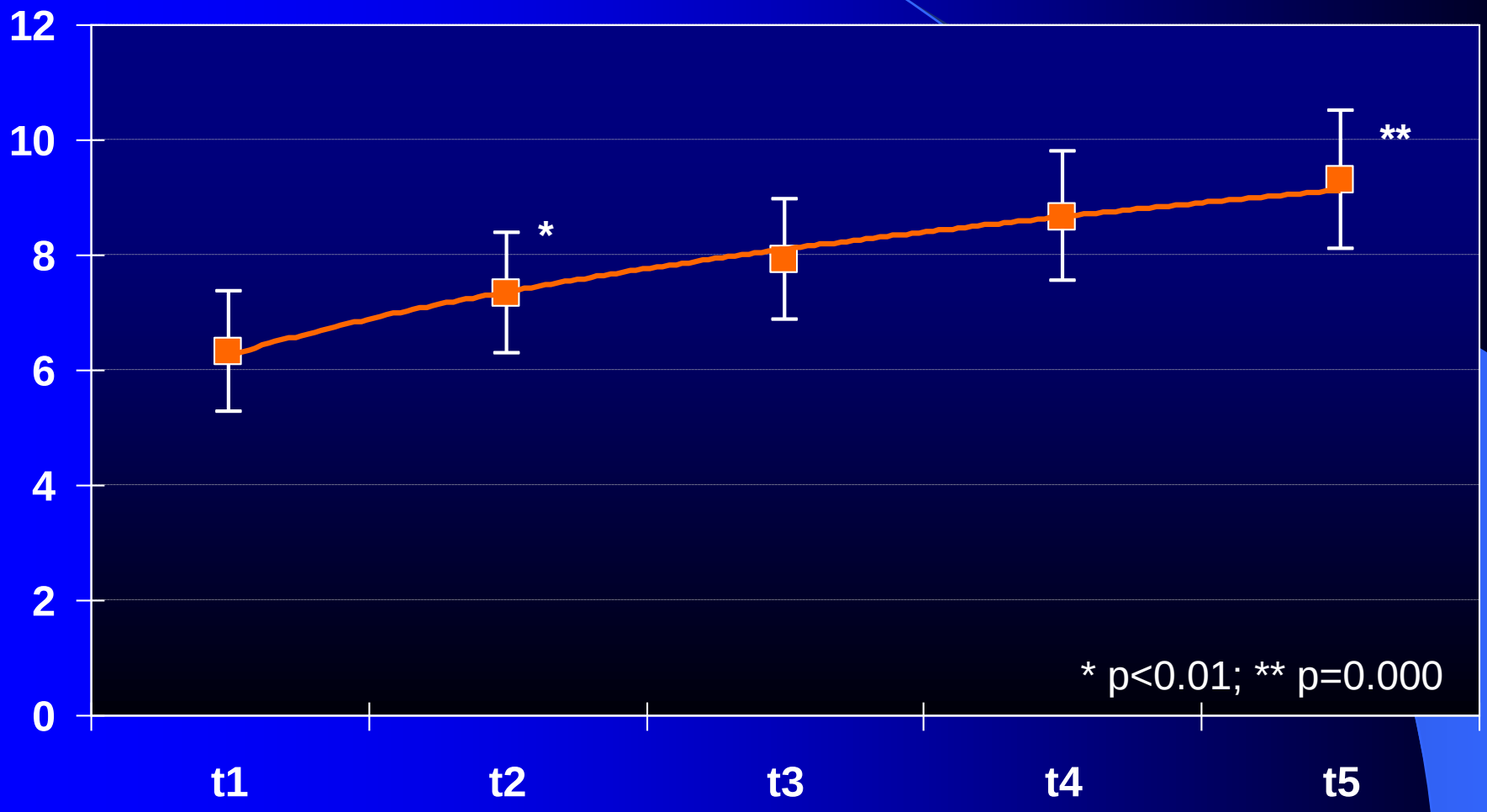


Paramete	Placebo		Testosterone		Analysis of the difference testosterone vs placebo (delta)		
	Baseline	Post	Baseline	Post treatment	Mean	p	95% confidence intervals
HOMA [1]	3.76 ±0.44	4.64 ± 0.98	4.25 ± 0.57	3.5 ± 0.52	-1.73 ± 0.67	**0.02**	-0.28 to –3.18
HbA1c	7.33 ± 0.18	7.39 ± 0.24	7.43 ± 0.19	7.13 ± 0.17	-0.37 ± 0.17	**0.03**	-0.03 to –0.71
Fasting insulin [1]	12.37 ± 1.87	12.36 ± 2.13	13.68 ± 1.95	11.76 ± 1.76	-1.9 ± 1.1	0.1	0.49 to –4.3
Fasting glucose	7.6 ± 0.43	8.73 ± 0.61	7.83 ± 0.49	7.38 ± 0.37	-1.58 ± 0.68	**0.03**	-0.17 to –2.99
Total cholesterol	4.95 ± 0.15	5.07 ± 0.17	5.11 ± 0.17	4.83 ± 0.2	-0.4 ± 0.17	**0.03**	-0.04 to –0.75
HDL cholesterol	1.04 ± 0.04	1.02 ± 0.04	1.02 ± 0.04	0.97 ± 0.04	-0.03 ± 0.04	0.3	-0.11 to 0.04
LDL cholesterol [2]	2.64 ± 0.16	2.81 ± 0.17	2.79 ± 0.15	2.74 ± 0.18	-0.23 ± 0.15	0.2	-0.55 to 0.1
Triglyceride	2.7 ± 0.2	2.76 ± 0.26	2.9 ± 0.25	2.56 ± 0.26	-0.4 ± 0.3	0.2	-1.03 to 0.23
Waist/ hip ratio	1.01± 0.01	1.02 ± 0.01	1.02 ± 0.01	1.003 ± 0.01	-0.03 ± 0.01	**0.01**	-0.048 to - 0.006
Waist circum (cm)	114.29 ± 2.4	114.38 ± 2.4	115.29 ± 2.4	113.75 ± 2.4	1.63 ± 0.71	**0.03**	0.15 to 3.1
% body fat	33.73 ± 1.04	33.14 ± 1.09	33.79 ± 1.13	32.77 ± 1.1	-0.85 ± 0.55	0.1	-1.99 to 0.29
BMI	32.85 ± 0.88	32.97 ± 0.95	33.28 ± 0.92	33.62 ± 0.91	0.23 ± 0.21	0.3	-0.2 to 0.66
Fat free mass	66.99± 2.17	67.66 ± 2.24	67.08 ± 2.17	68.31 ± 2.14	0.56 ± 0.76	0.4	-1.01 to 2.13
Systolic BP	131 ± 3.1	127.5 ± 2.9		127.6 ± 2.8	0.43 ± 2.7	0.8	-5.18 to 6.05
Diastolic BP	74 ± 1.4	72.7 ± 1.7		72.6 ± 1.5	0.26 ± 1.5	0.8	-2.7 to 3.2

Androgen deprivation treatment for Prostate Cancer in Diabetic Men

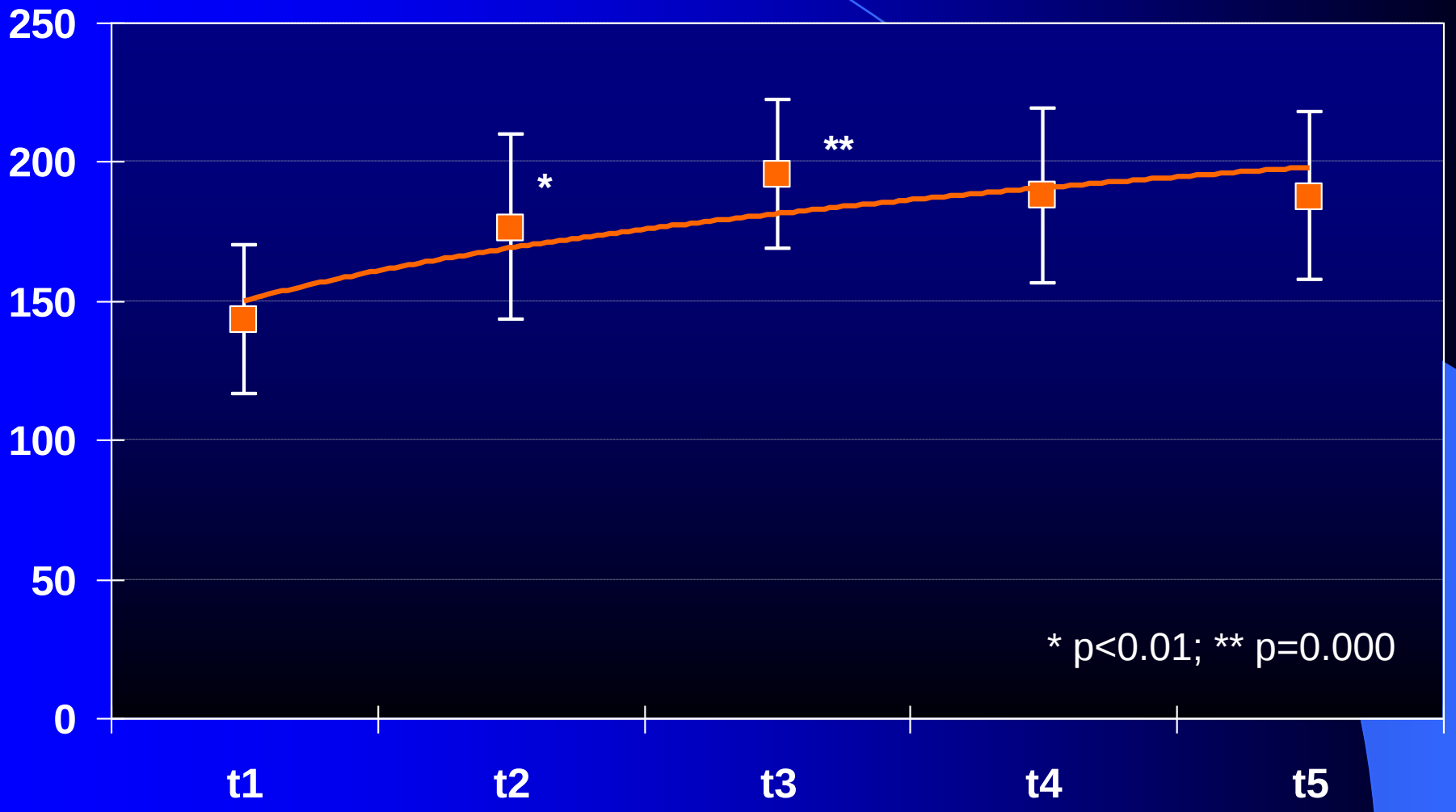
29 men followed for 3 months post GnRH analogue therapy for prostate cancer

HbA_{1c} (%) in 29 Diabetic Prostate Cancer Patients under Androgen Deprivation Therapy (norm value: 4.2-5.8 %)



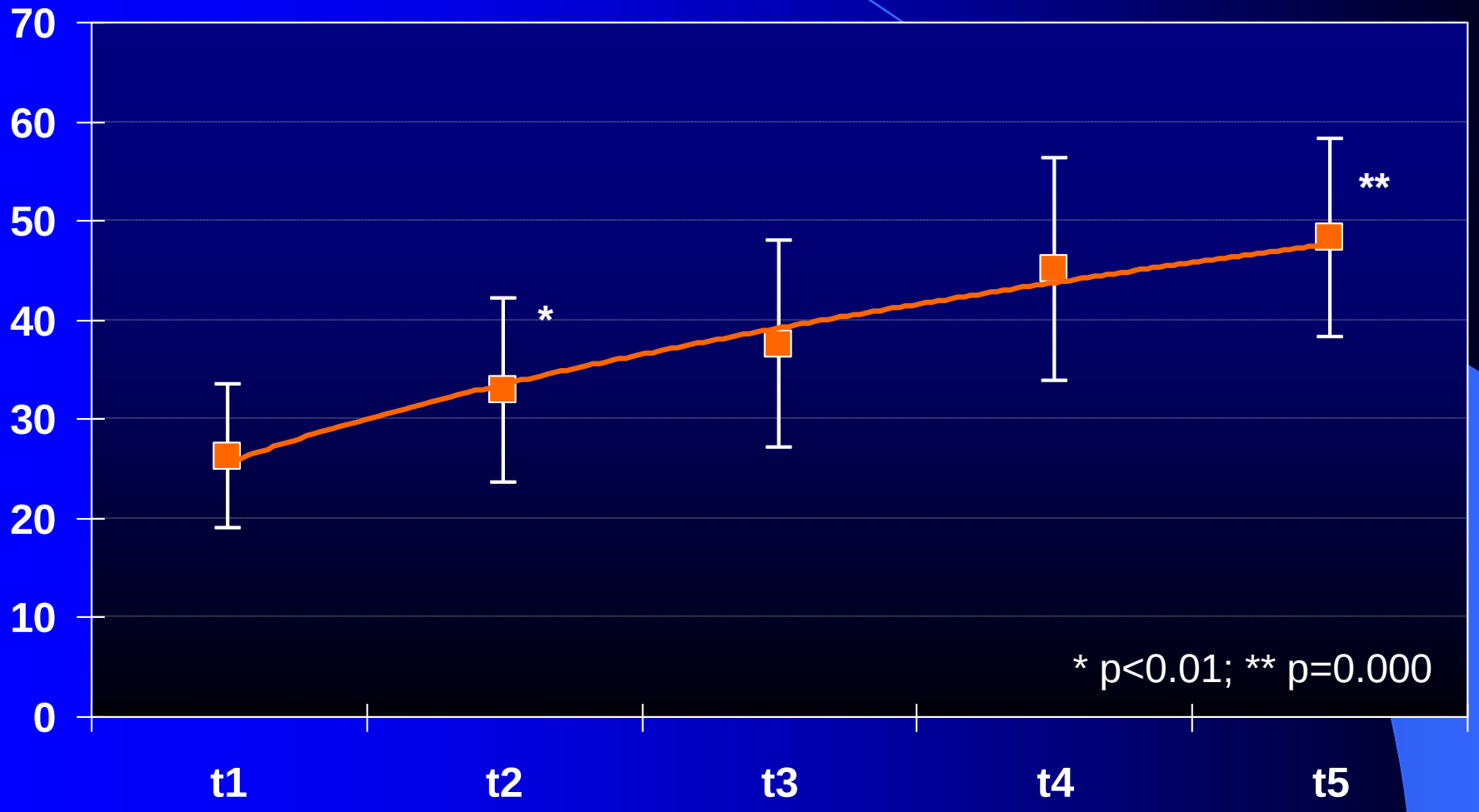
Yassin A et al. J Urol 175(4, Suppl.): 385 (2006)

Fasting Glucose (mg/dL) in 29 Diabetic Prostate Cancer Patients under Androgen Deprivation Therapy (norm value: 75-110 mg/dL)



Yassin A et al. J Urol 175(4, Suppl.): 385 (2006)

Insulin Requirement (Units) in 29 Diabetic Prostate Cancer Patients under Androgen Deprivation Therapy



Yassin A et al. J Urol 175(4, Suppl.): 385 (2006)

Diabetes and Cardiovascular Disease during Androgen Deprivation Therapy for Prostate Cancer

- 73,196 men (66yrs+) followed from 1992-1999 with cancer confined to the prostate
- 1/3rd treated GnRH analogues
- Increased risk of :-

Incident Diabetes	HR 1.4,	p<0.01
CHD	HR 1.16	p<0.01
MI	HR 1.11	p=0.03
Sudden Cardiac Death	HR 1.16	p<0.01

HR = Hazard Ratio

Keating et al., J Clin Oncology 2006; 24: 4448-56

Erectile Dysfunction

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**

Risk Factors Associated with Erectile Dysfunction

	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%0	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

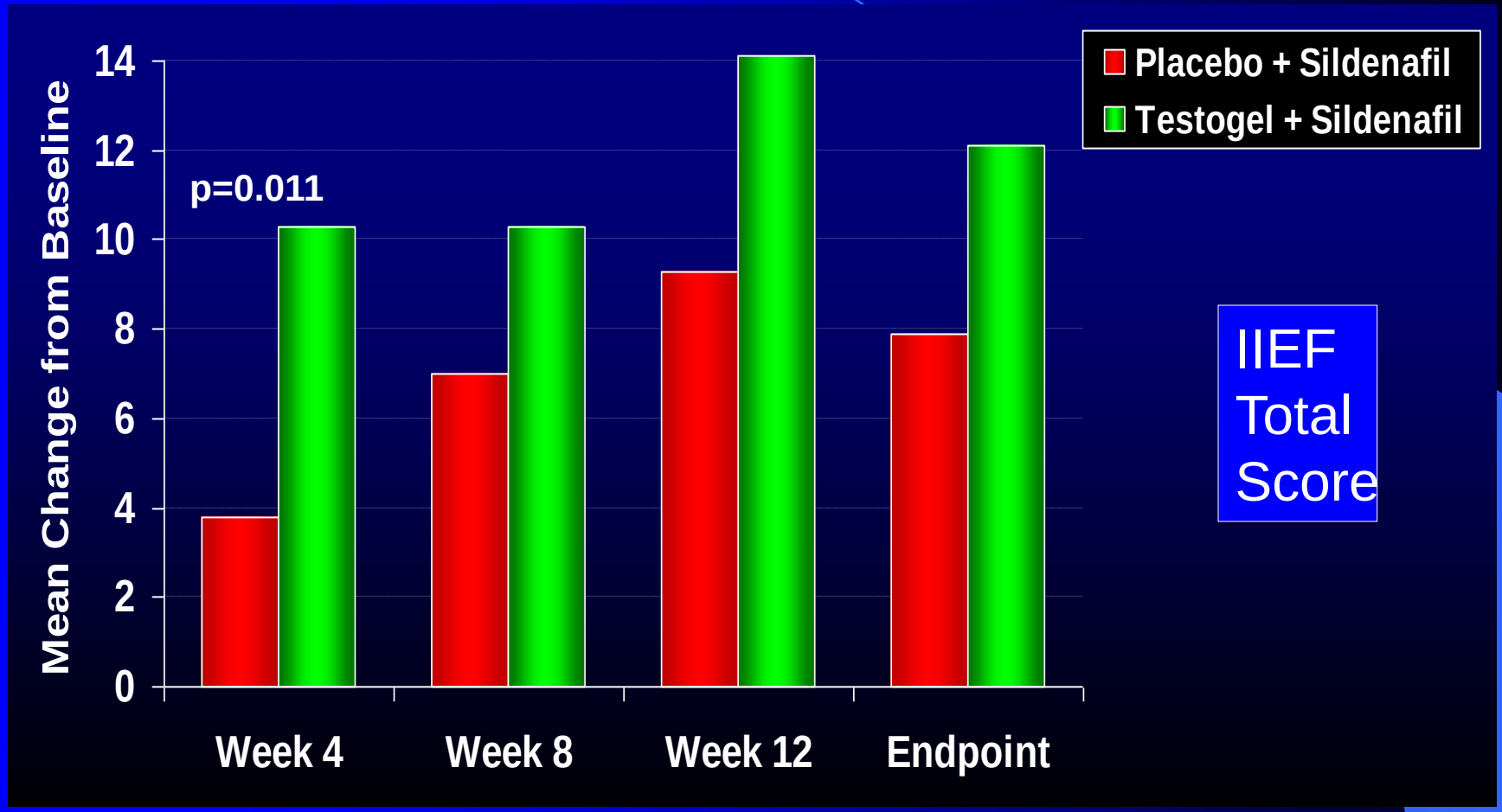
The Role of Androgens in Erectile Function

T levels in Viagra nonresponders and responders at baseline (men with Diabetes)

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

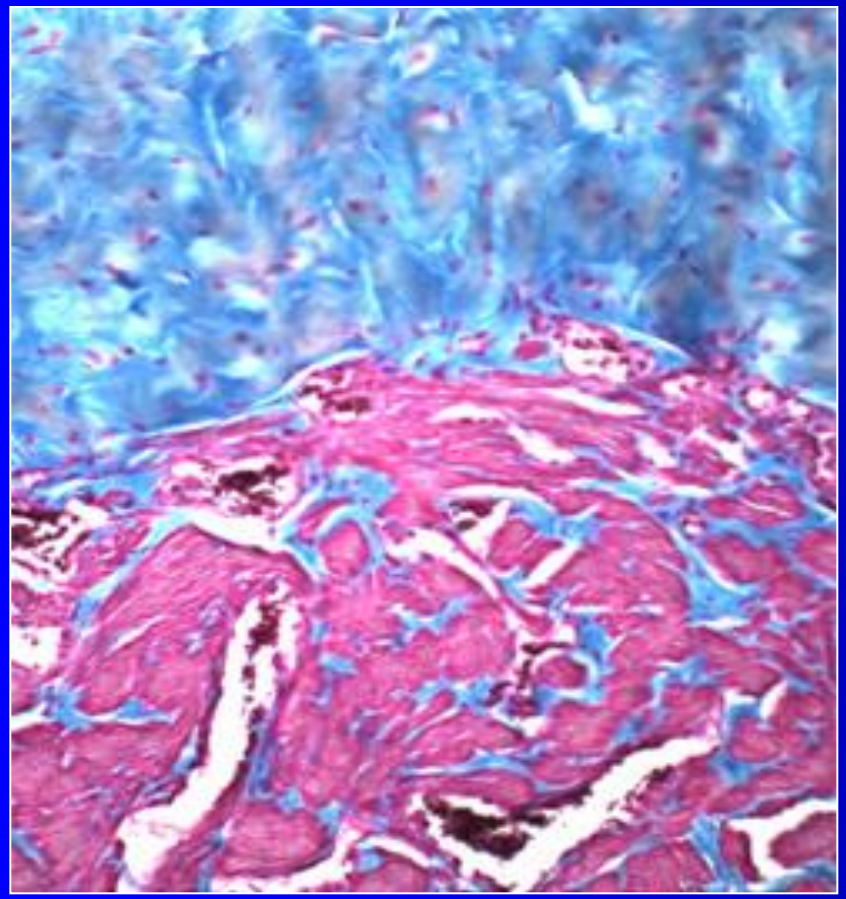
Kalinchenko S et al. Aging Male 6: 94-99 (2003)

Testosterone Therapy (5g Testogel®/d/12 wk) Converts Sildenafil 100 mg Non-responders to Responders in Men with Hypogonadism and ED

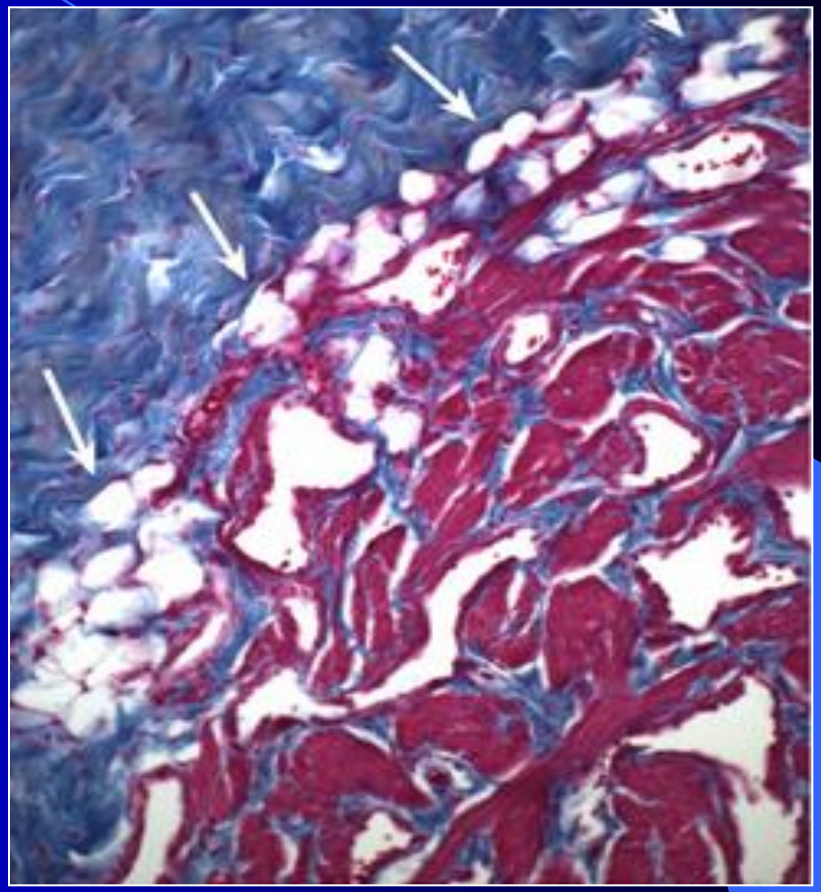


Shabsigh R et al. J Urol 169(4) Suppl.: 247 (2003)

Testosterone Deprivation Promotes Adipocyte Accumulation in the Penile Corpus Cavernosum in the Rabbit Model



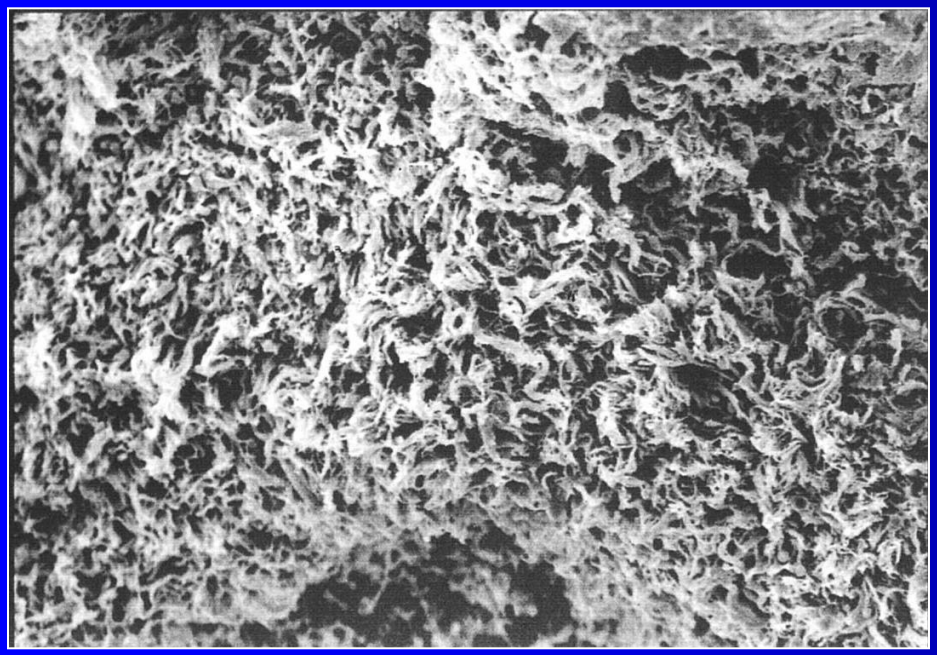
Control



Castrated

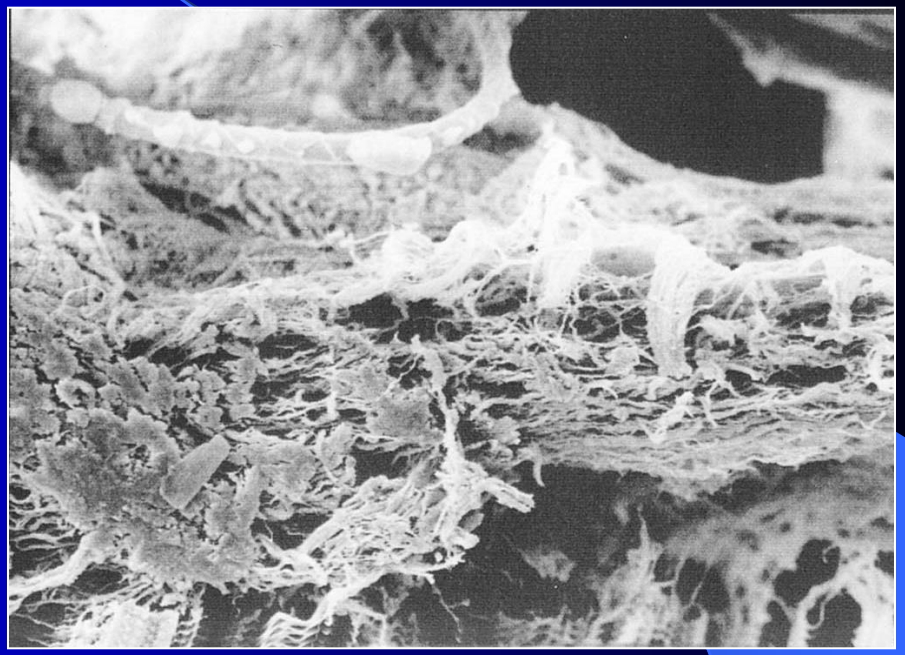
Traish A et al. J Androl 26(2): 88-94 (2005)

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



Group A:

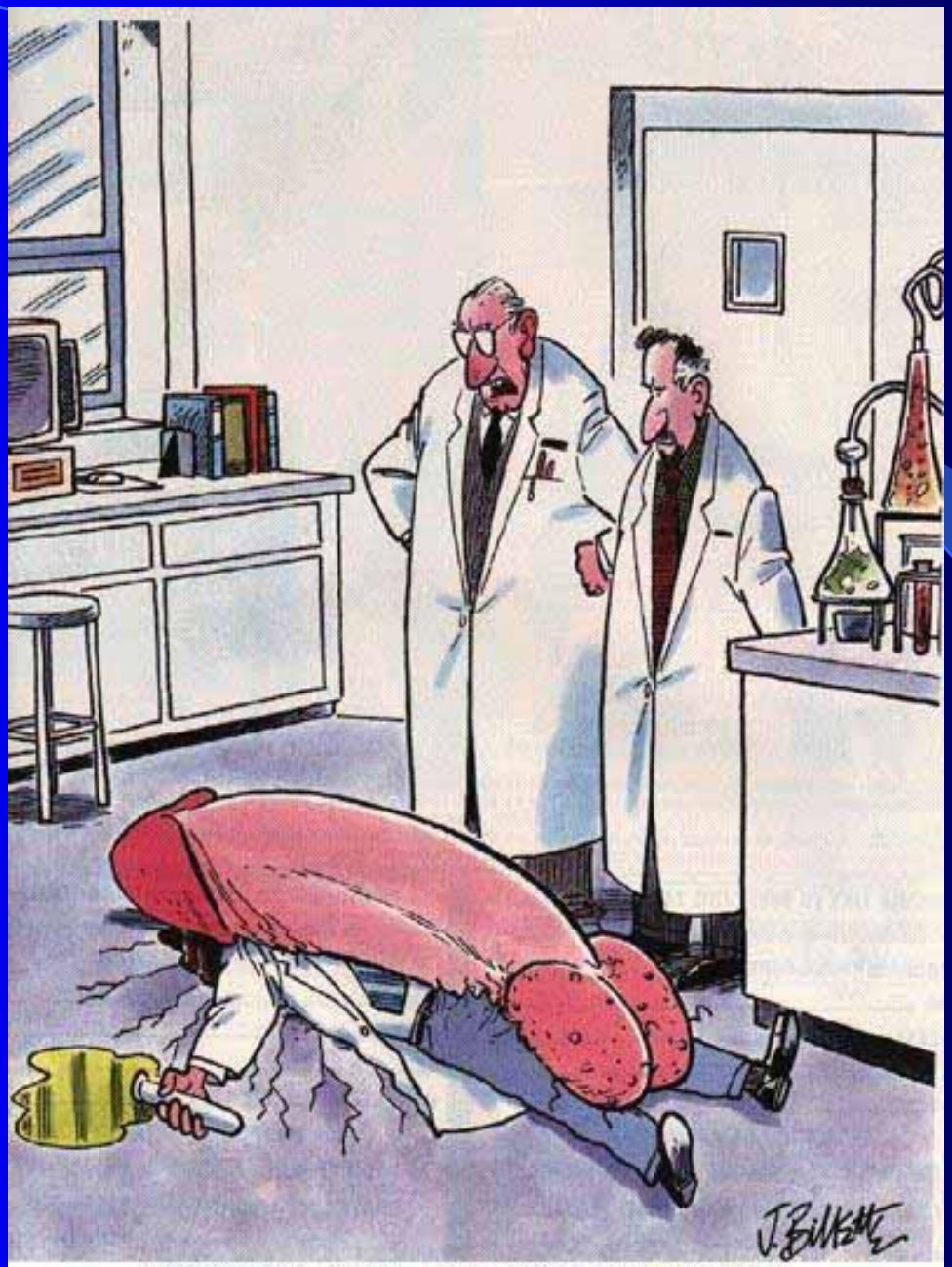
Control rich, regularly arranged elastic fibers



Group B:

Castrated (4 weeks) elastic fibers replaced by collagenous fibers

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



"Damned if I know ... something called Viagra."

Angina

Testosterone for Heart Attack

July 6, 1942
Vol. XL No. 1

‘There is no cure for angina pectoris (heart attack), which afflicts hundreds of thousands in the U.S., but its agonizing pains have been relieved in a number of cases by injections of testosterone propionate, a male sex hormone. So reported Dr. Leslie Hamm of Boston in the current issue of the Journal of Clinical Endocrinology, in a review of his own work and that of Dr. Maurice Aaron Lesser. One of the most excruciating ailments known to medicine, angina usually comes on after an emotional shock or physical effort.’

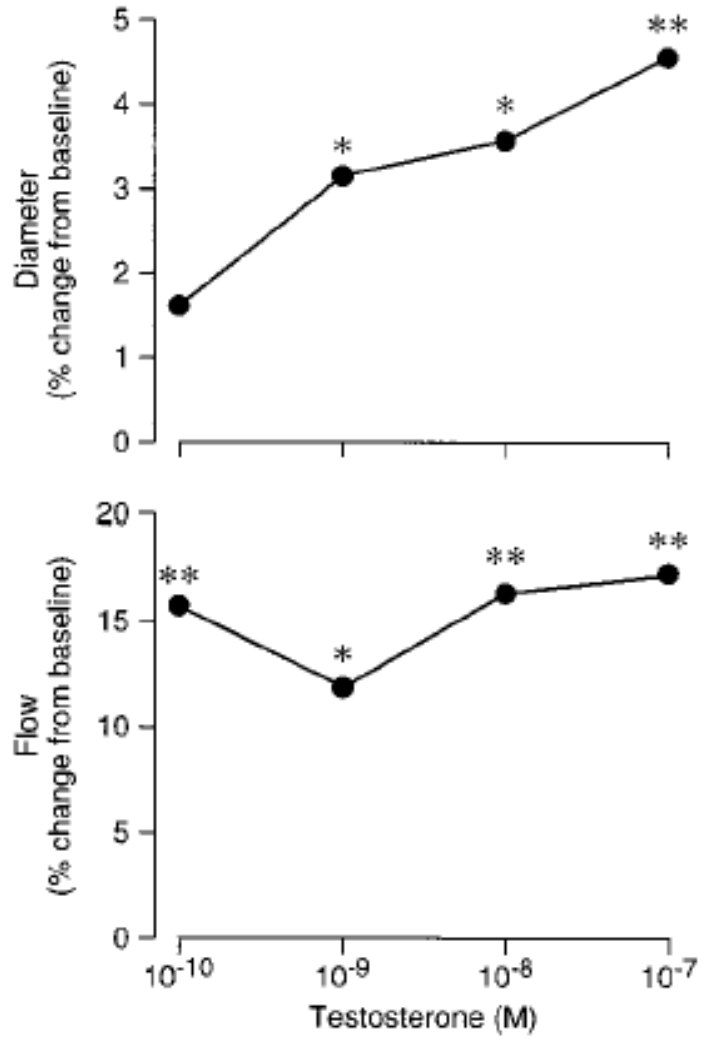
Effects of Testosterone on Coronary Vasomotor Regulation in Men With Coronary Heart Disease

Carolyn M. Webb, PhD; John G. McNeill, DCRR; Christopher S. Hayward, MB, BS, FRACP; Dominique de Zeigler, MD; Peter Collins, MD, FRCP

Circulation 1999; 100: 1690-1696

13 men with proven CAD

- coronary angiography
- Intra-coronary infusion of titrated doses of testosterone (10^{-10}, 10^{-9}, 10^{-8} & 10^{-7} M)
- Measurement of Coronary Artery Diameter
- Measurement of Coronary Blood Flow



Testosterone-induced increases in coronary artery diameter (top) and blood flow (bottom). $^{*}P<0.05$ and $^{**}P<0.01$ compared with baseline 2.

Webb *et al*,
Circ. 1999, 100, 1690-96

Low-Dose Transdermal Testosterone Therapy Improves Angina Threshold in Men With Chronic Stable Angina

A Randomized, Double-Blind, Placebo-Controlled Study

Katherine M. English, MBChB, MRCP; Richard P. Steeds, MBBS, MRCP;
T. Hugh Jones, MD, MRCP; Michael J. Diver, PhD; Kevin S. Channer, MD, FRCP

Background—Experimental studies suggest that androgens induce coronary vasodilatation. We performed this pilot project to examine the clinical effects of long-term low-dose androgens in men with angina.

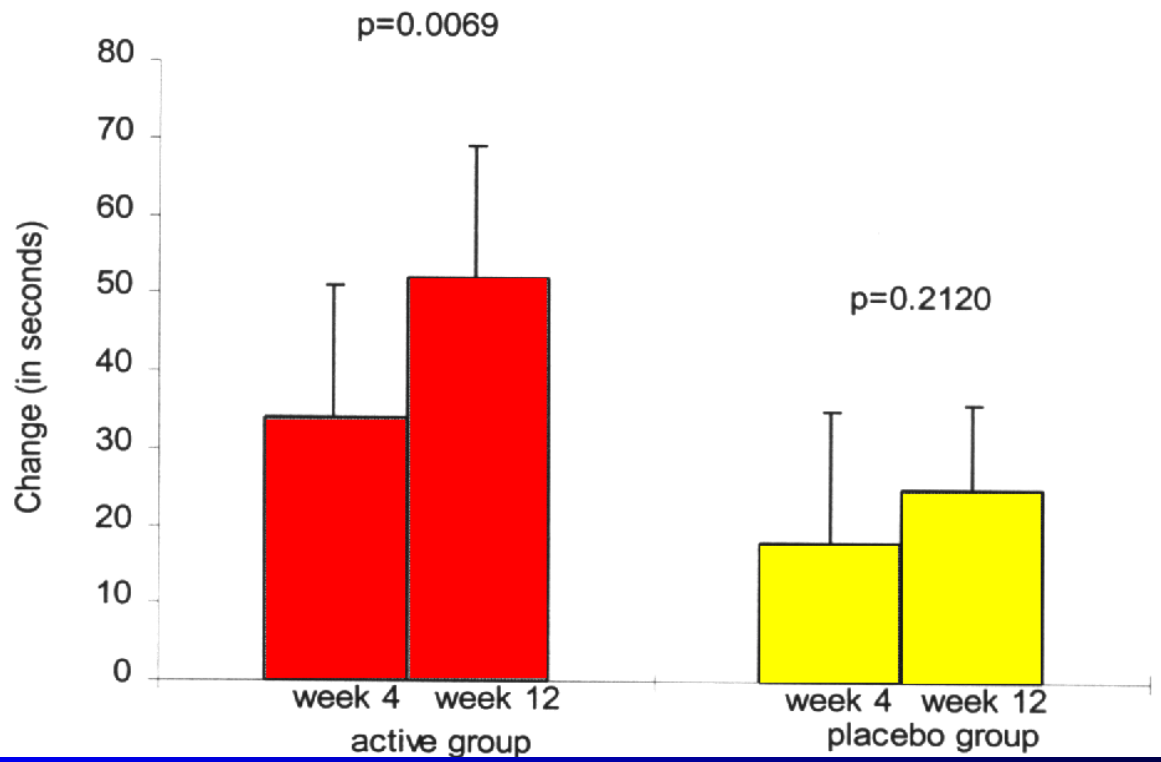
Methods and Results—Forty-six men with stable angina completed a 2-week, single-blind placebo run-in, followed by double-blind randomization to 5 mg testosterone daily by transdermal patch or matching placebo for 12 weeks, in addition to their current medication. Time to 1-mm ST-segment depression on treadmill exercise testing and hormone levels were measured and quality of life was assessed by SF-36 at baseline and after 4 and 12 weeks of treatment. Active treatment resulted in a 2-fold increase in androgen levels and an increase in time to 1-mm ST-segment depression from (mean±SEM) 309±27 seconds at baseline to 343±26 seconds after 4 weeks and to 361±22 seconds after 12 weeks. This change was statistically significant compared with that seen in the placebo group (from 266±25 seconds at baseline to 284±23 seconds after 4 weeks and to 292±24 seconds after 12 weeks; $P=0.02$ between the 2 groups by ANCOVA). The magnitude of the response was greater in those with lower baseline levels of bioavailable testosterone ($r=-0.455$, $P<0.05$). There were no significant changes in prostate specific antigen, hemoglobin, lipids, or coagulation profiles during the study. There were significant improvements in pain perception ($P=0.026$) and role limitation resulting from physical problems ($P=0.024$) in the testosterone-treated group.

Conclusions—Low-dose supplemental testosterone treatment in men with chronic stable angina reduces exercise-induced myocardial ischemia. **(*Circulation*. 2000;102:1906-1911.)**

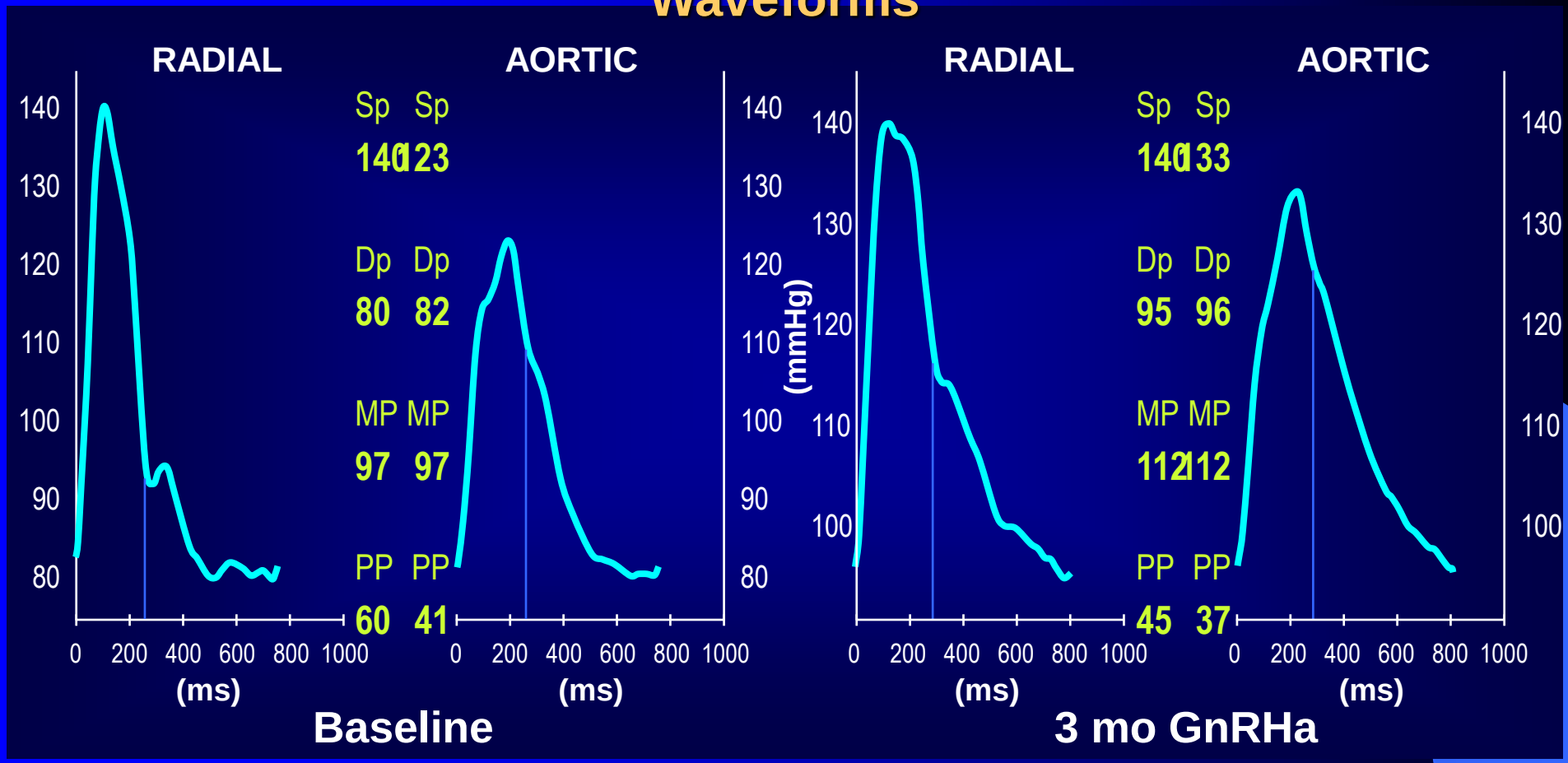
Key Words: testosterone ■ hormones ■ angina ■ ischemia

Circulation 2000; 102:1906-11

Change in Seconds from Baseline to 1mm ST Depression



Induced Hypogonadism (3 mo GnRHa) Results in Large Artery Stiffening in Men with Prostate Cancer Demonstrated in Peripheral and Central Arterial Waveforms

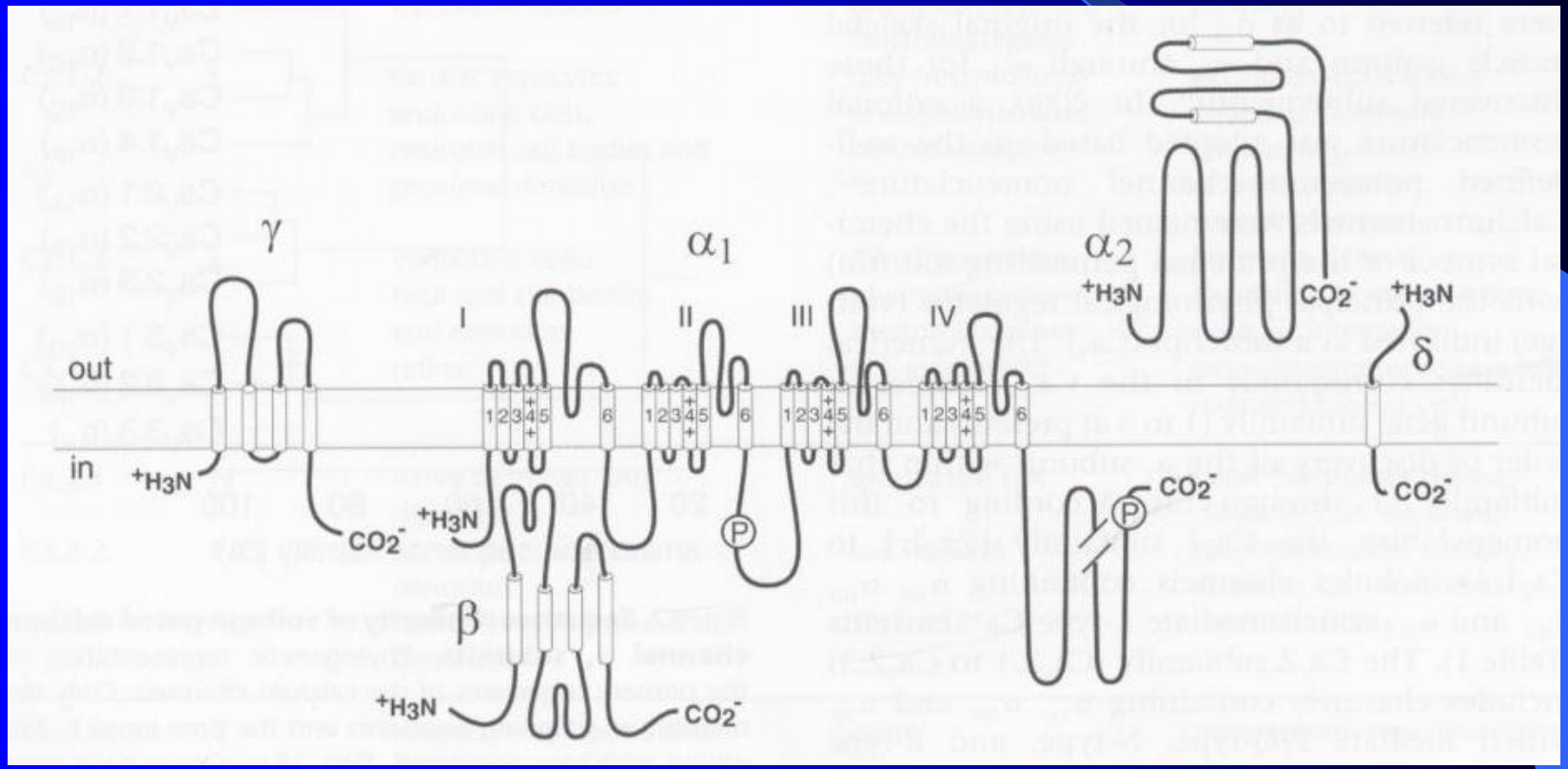


Smith JC et al. J Clin Endocrinol Metab 86(9): 4261-4267 (2001)

Mechanism of the Vasodilatory Action of Testosterone

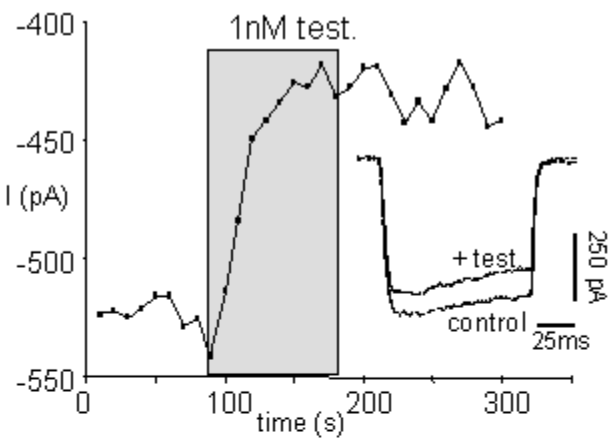
- Endothelium independent
- Direct action on Smooth Muscle Cell
- Non-genomic
- Independent of Classic Androgen Receptor (*Jones R et al. JEnd 2002*)
- Binds to Cell Membrane
- Calcium antagonist (*English et al. JEndInvest 2002)*
- L Calcium Channel Blocker

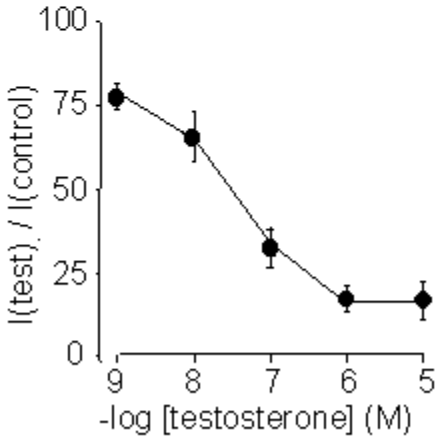
L-Calcium Channel Structure

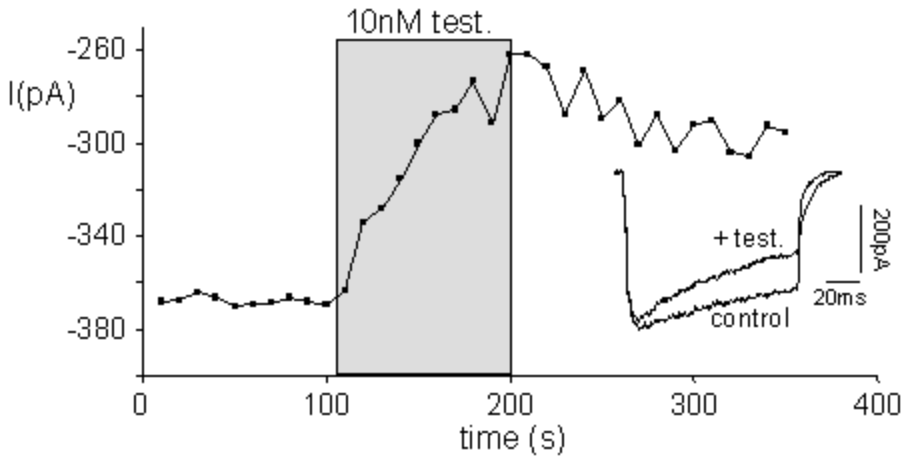


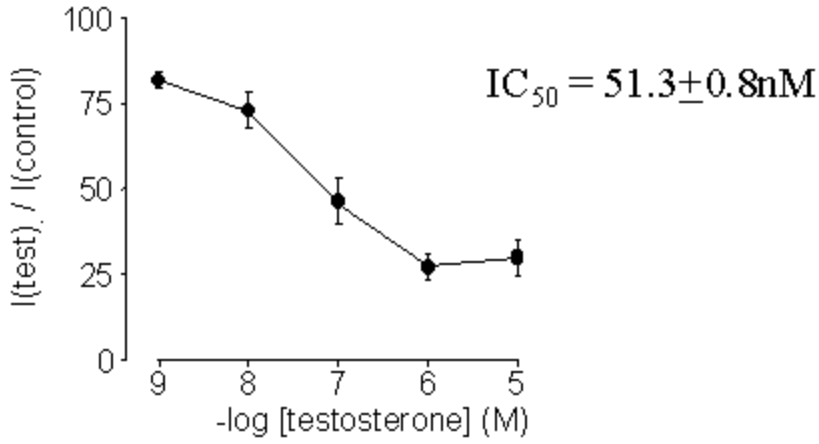
1) HEK293 cells stably expressing the α_{1C} subunit of the L-type VGCC ($Ca_v1.2$).

2) A7r5 vascular smooth muscle cells expressing native $Ca_v1.2$ L-type VGCCs.

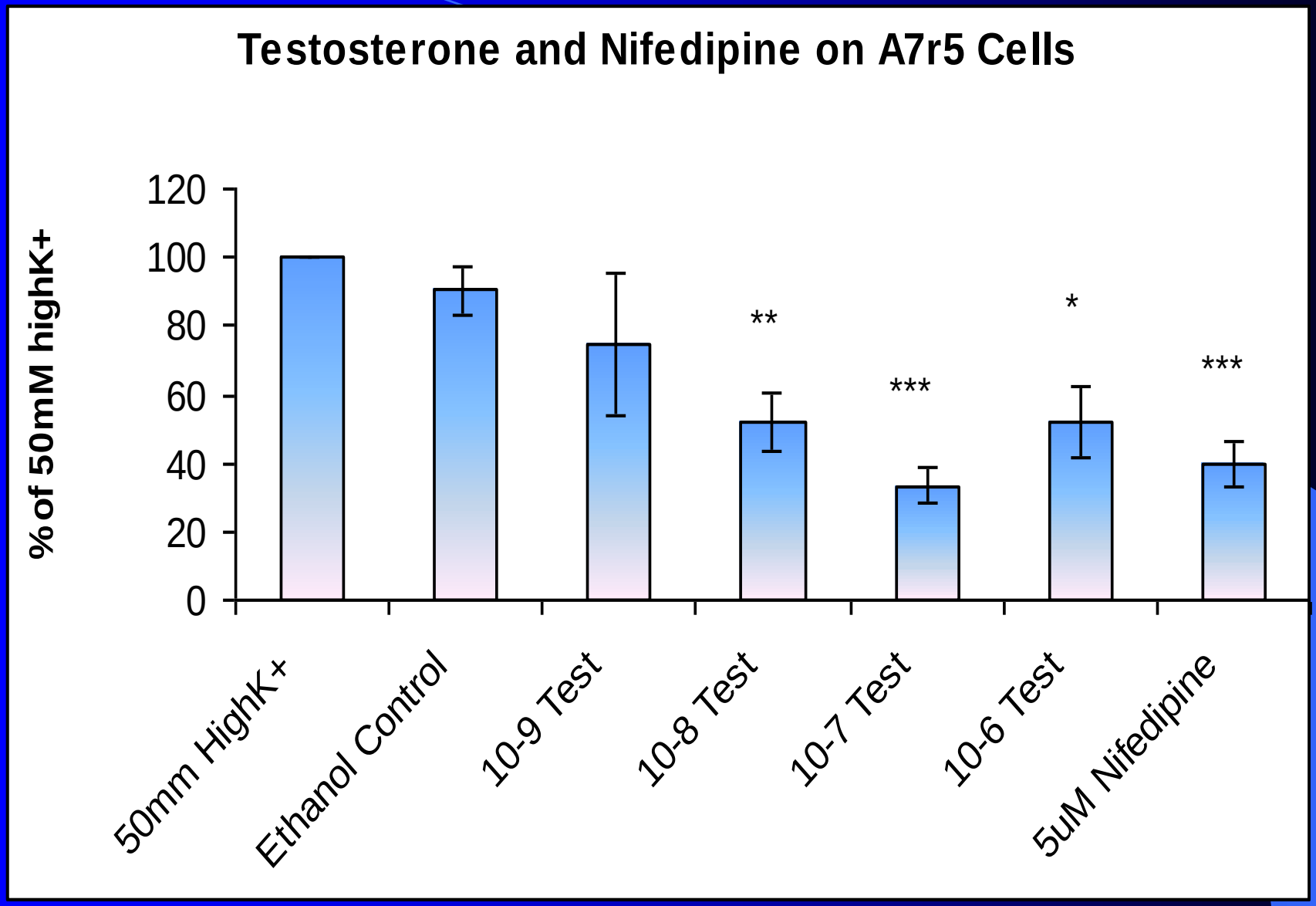


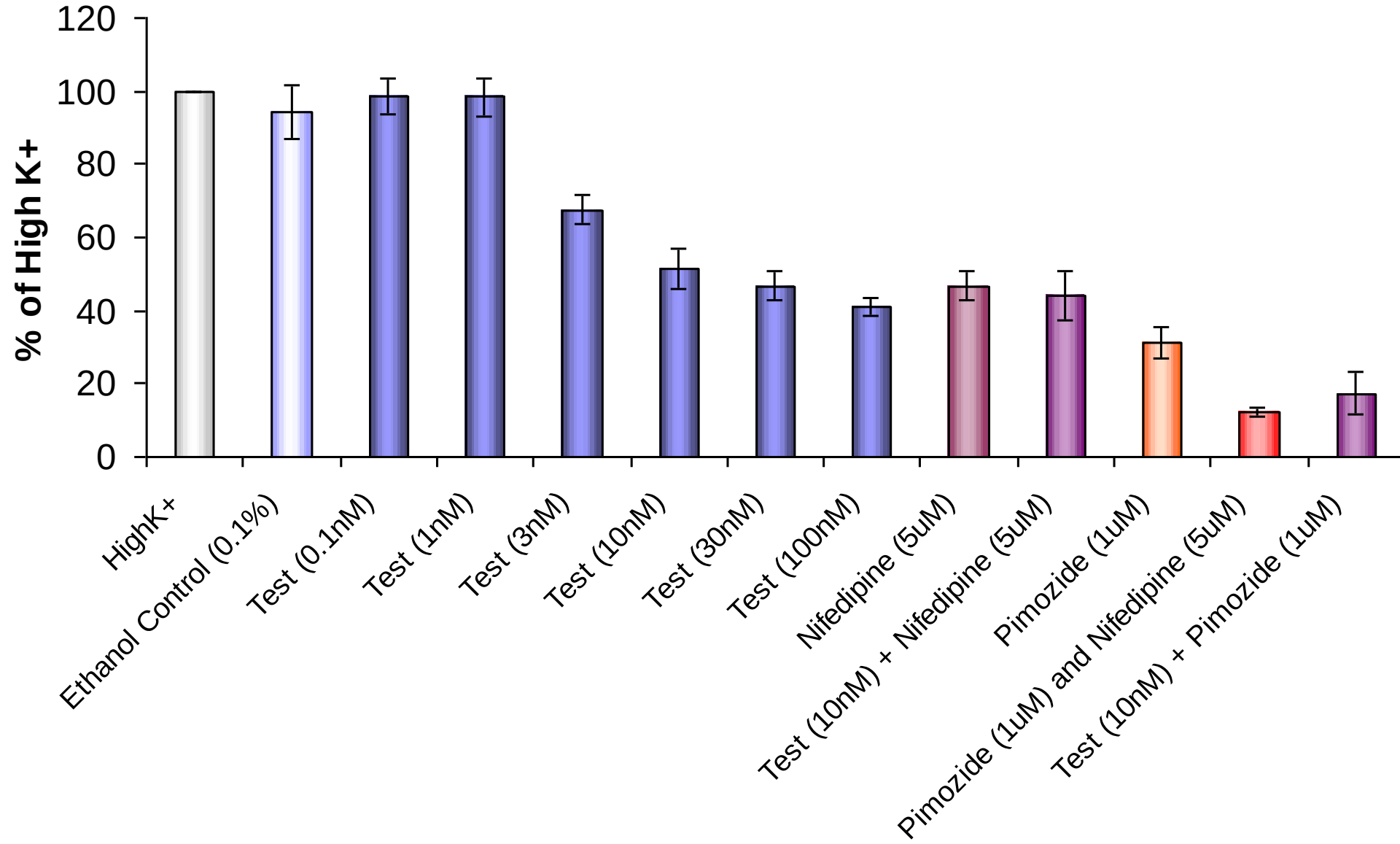






Effect of Testosterone and Nifedipine on Intracellular Calcium Fluoresence in A7r5 Cells


Testosterone and Nifedipine on A7r5 Cells
% of 50mM highK+
120
100
80
60
40
20
0
**
***
*
***
50mm HighK+
Ethanol Control
10-9 Test
10-8 Test
10-7 Test
10-6 Test
5uM Nifedipine


% of High K+
120
100
80
60
40
20
0
HighK+
Ethanol Control (0.1%)
Test (0.1nM)
Test (1nM)
Test (3nM)
Test (10nM)
Test (30nM)
Test (100nM)
Nifedipine (5uM)
Test (10nM) + Nifedipine (5uM)
Pimozide (1uM)
Pimozide (1uM) and Nifedipine (5uM)
Test (10nM) + Pimozide (1uM)

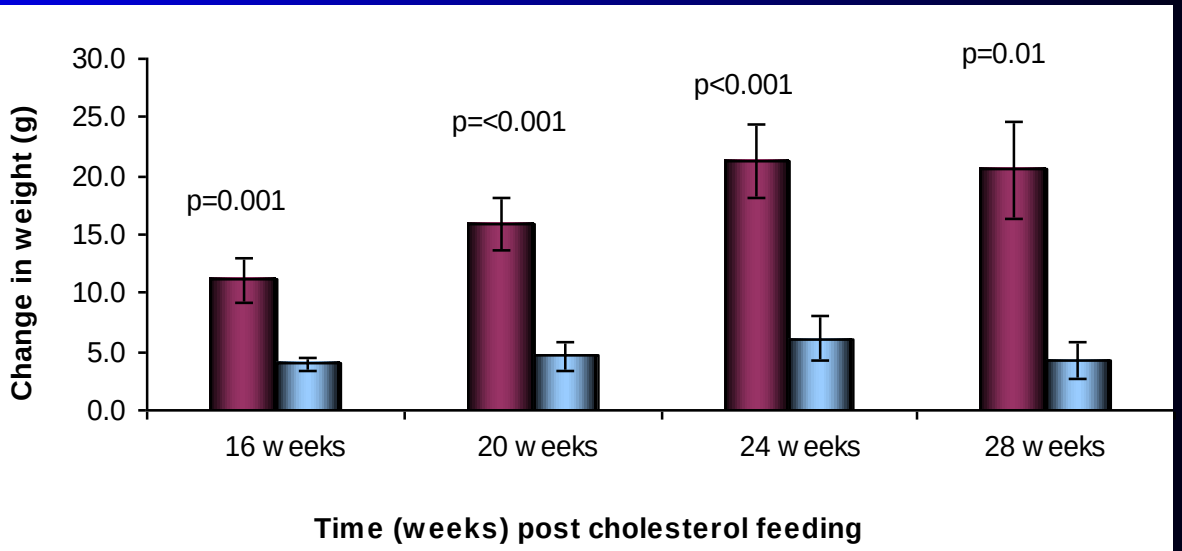
Atherosclerosis

Testicular Feminised Mouse

- Tfm male has an inactive androgen receptor and low levels of circulating testosterone (17alpha hydroxylase deficiency)
- Wild type littermate control

Cholesterol feeding study

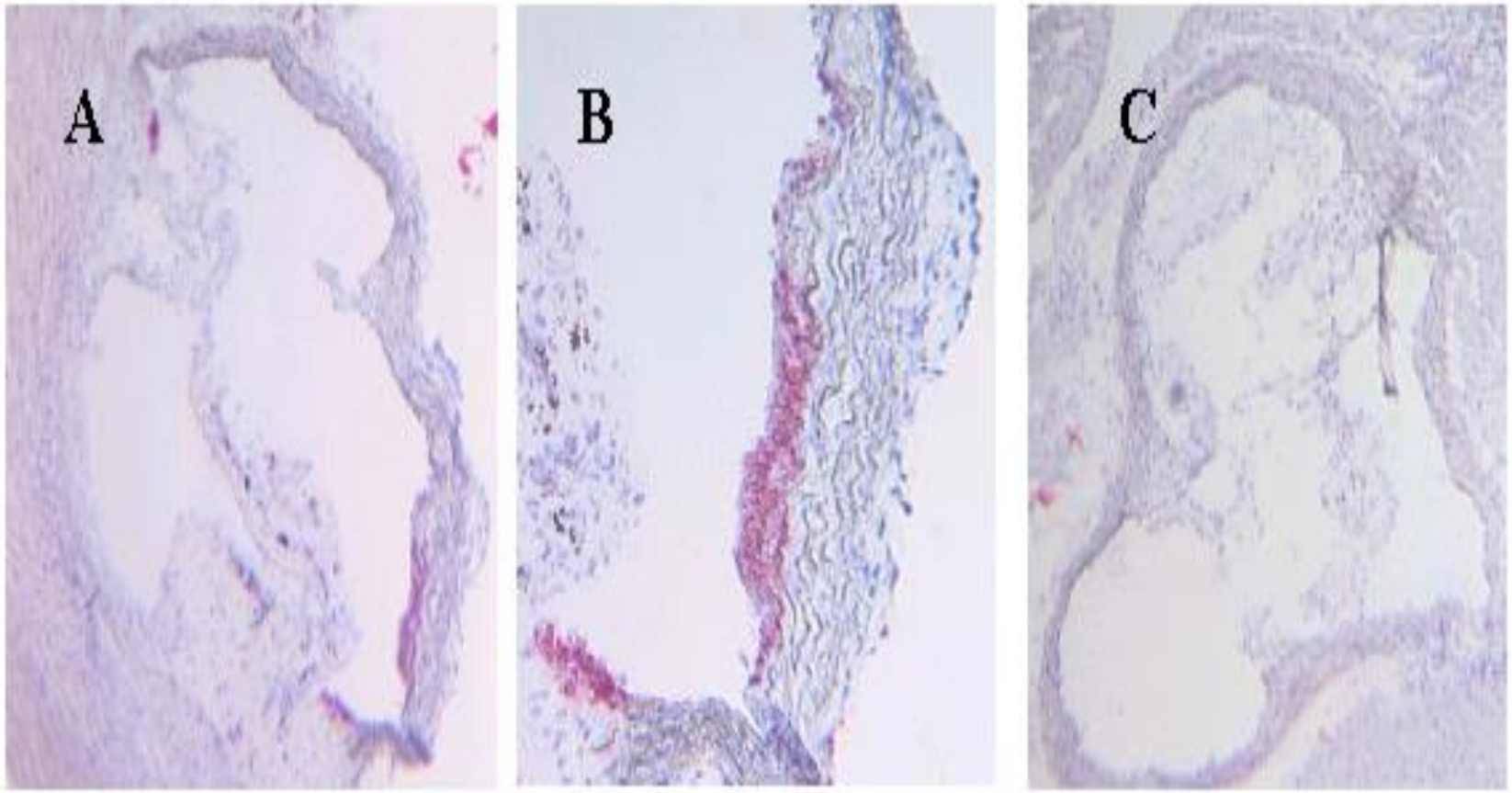
Weight gain following cholesterol-feeding period



$X^{Tfm}Y$

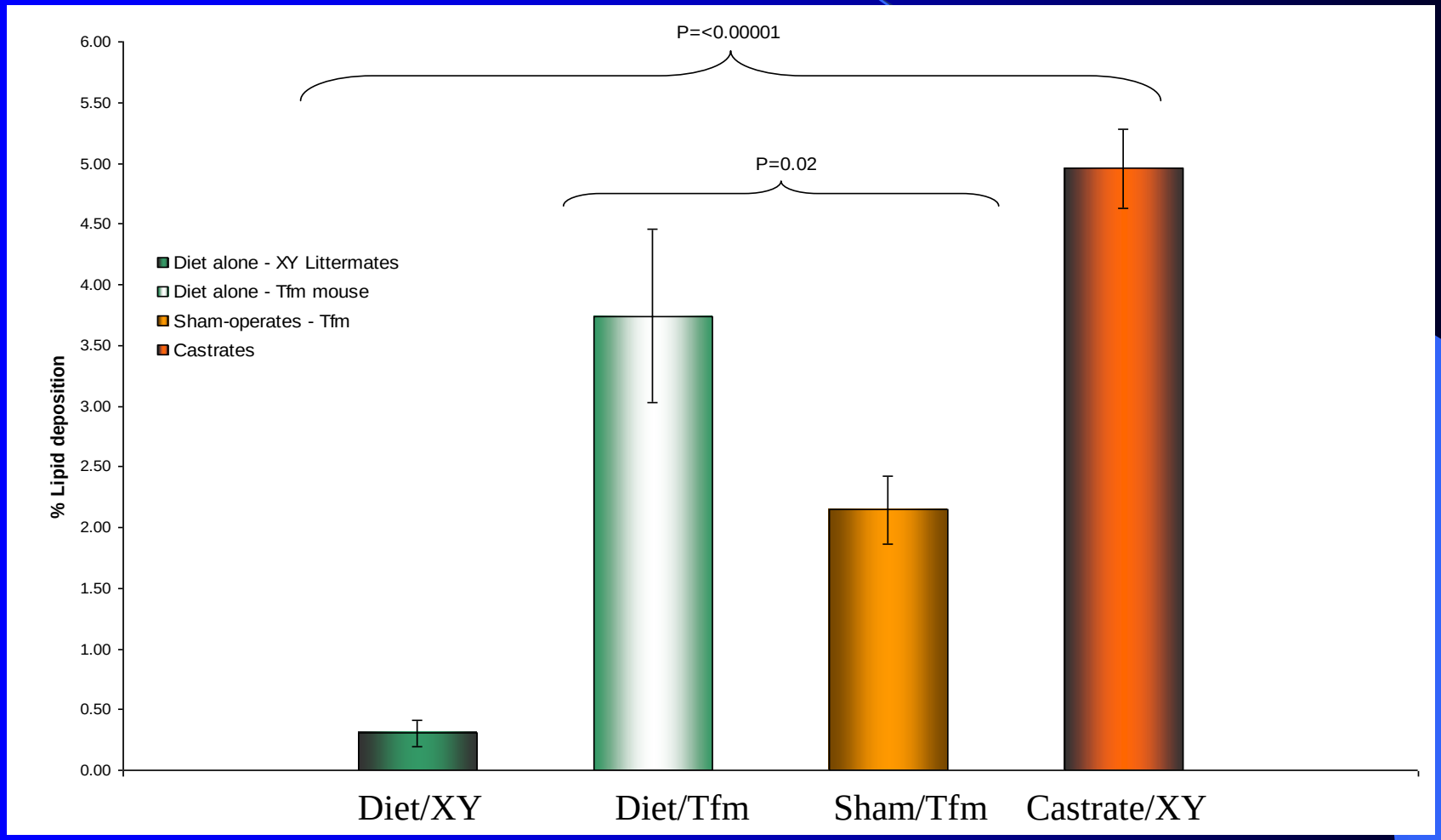
XY littermate

Aortic Root Lipid Deposition after 28 weeks High Cholesterol Diet

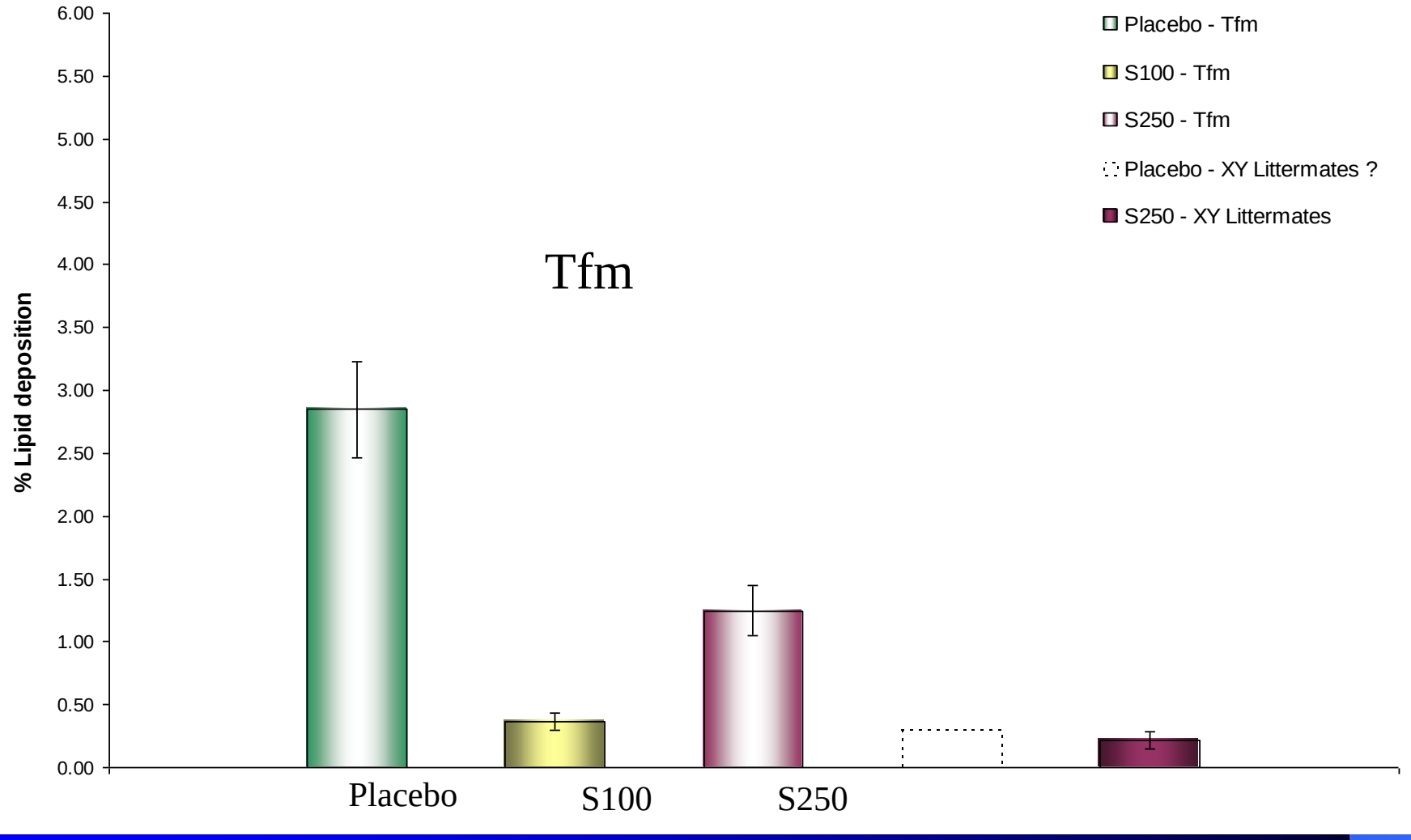


Tfm | Tfm (High Magnification) | Wild Type

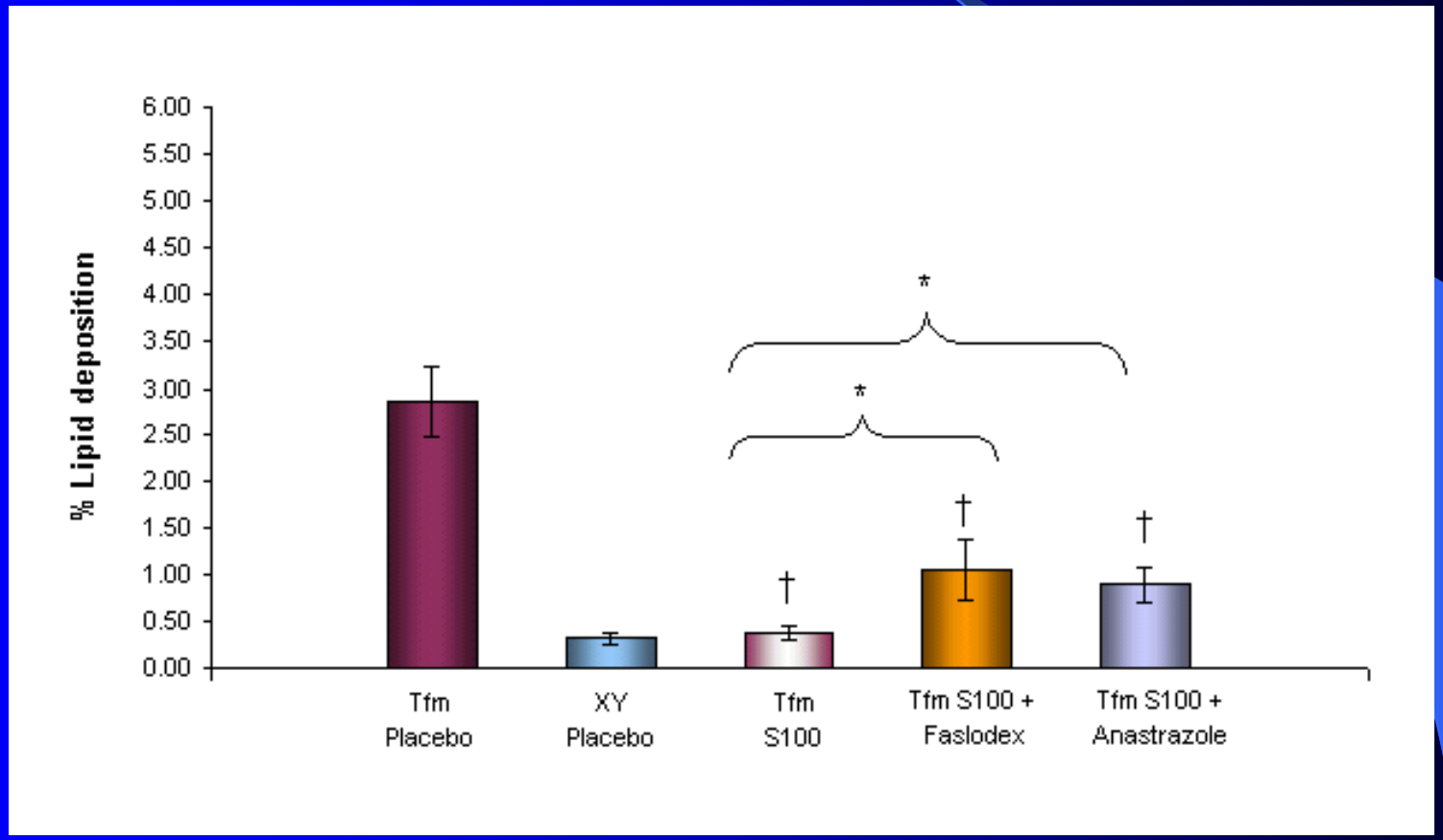
Effect of Diet and Castration on Tfm and XY Littermate Control



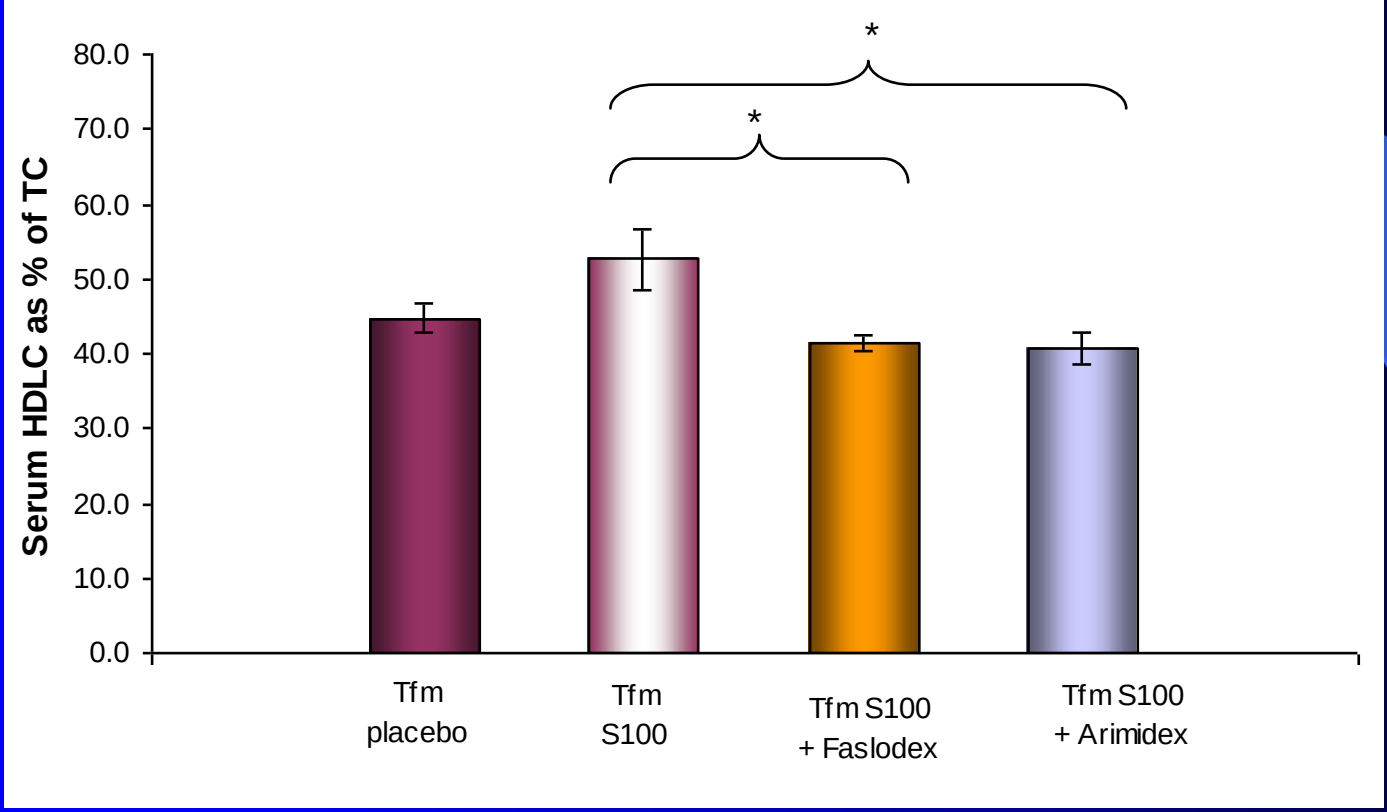
Effect of Physiological and Supraphysiological TRT on Lipid Plaque Formation in Tfm mouse



Effect of E2 receptor antagonist (Faslodex) & Aromatase Inhibitor (Anastrazole) on Testosterone Therapy for Protection of Lipid Plaque Development in the Tfm Mouse



Effect of Testosterone on HDLcholesterol in Tfm



P < 0.05

Summary

- Low Testosterone Levels in men with Type 2 Diabetes
- Association of low T with Visceral Obesity
- TRT leads to reduction in visceral obesity and insulin resistance with improvement in glycaemic control
- Any factor which reduces insulin resistance should reduce overall cardiovascular risk
- Larger, longer term studies are needed to investigate this further!


Emperor penguins, Antarctica
Photograph © Fred Oliver
bbc.co.uk/planetearth

Group Heads

Hugh Jones (Endocrinology)

Kevin Channer (Cardiology)

Postdoctoral Research Scientist

Richard Jones

Clinical Research Fellows

Kate English
Dheeraj Kapoor
Chris Malkin
Peter Pugh
Alyson Smith
Roger Stanworth

PhD Students

Joanne Hall
Katherine Kerry
Joanne Nettleship

Current Collaborators

Institute for Cardiovascular Research
University of Leeds

Chris Peers
Jason Scragg

Department of Surgery
Sheffield Teaching Hospitals

Ian Adam
Andrew Shorthouse

Department of Cardiothoracic Surgery
Hull & East Yorkshire Hospitals

Mike Cowen
Rob Bennett

Case History 1

- J.S. 64 years
- No libido, reduced energy to point unable to work.
- PMH Type 2 Diabetes, Ischaemic heart Disease, Hypertension
- O/E BMI 33, Waist circumference 101cm

Investigations

- Testosterone 6.1, 5.1, 7.6 nmol/l
- LH 5.2 iu/l
- FSH 6.7 iu/l
- SHBG 20.8 nmol/l
- BMD Osteopaenia Hip and Lumbar Spine

Diagnosis/Management

- Mixed Hypogonadism
- Treated with Testosterone
- 3/12 later feels new man. Back working as a roof tiler.

Case History 2

- J.L. 56 yrs
- Erectile dysfunction gradual onset over 2 years. No response to sildenafil so treatment stopped.
- 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

- Testosterone
- 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.

Case 3

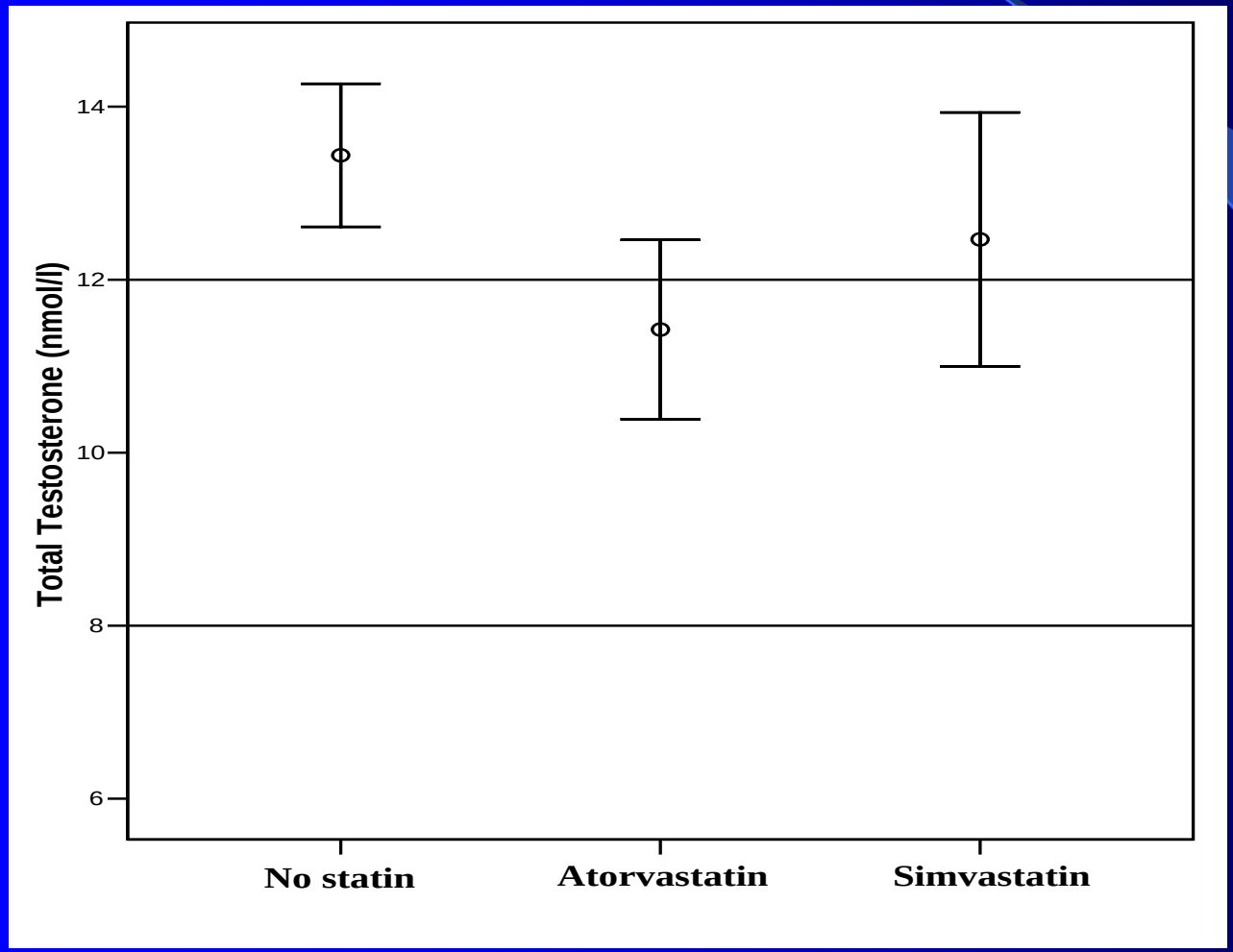
- 67 year old man presented with a history of exertional angina 2-3 times per week.
- Non-smoker, BMI 31, No other cardiovascular risk factors.
- On systematic enquiry he was found to have erectile dysfunction, non-existent libido and fatigue.
- Drug History Atenolol,Aspirin, Nicorandil and simvastatin.

Investigations

- 0900h Total T 8.7nmol/l, 7.4nmol/l
- SHBG 26.2 nmol/l (15-75)
- FSH 6.6iu/l (2-12)
- LH 4.5iu/l (2-12)
- Prl 120mU/l

- Commenced on Testosterone
- Symptom of fatigue completely resolved.
- Good libido
- Stronger erections
- Angina frequency and intensity improved
- Testosterone level 20.3nmol/l

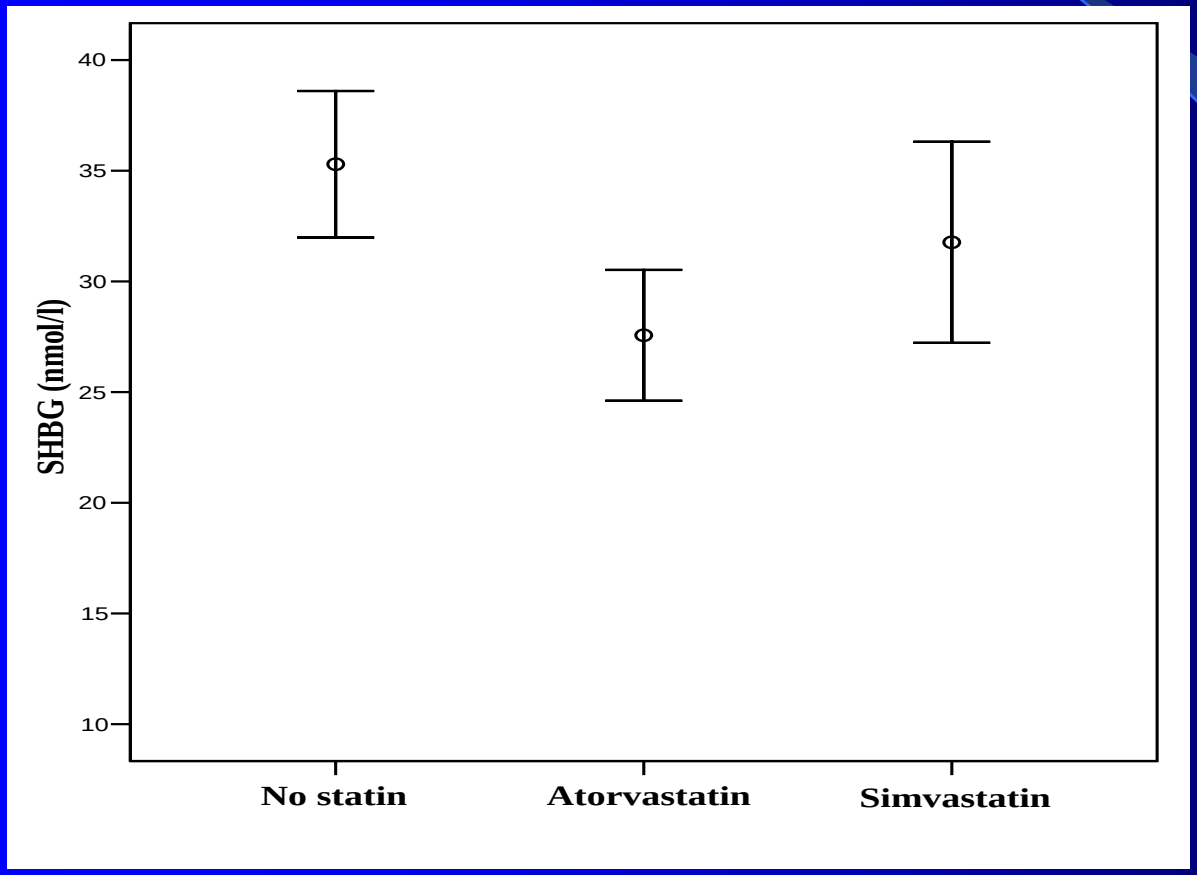
Total testosterone vs statin use



Atorvastatin vs No Statin p=0.006

Simvasatin vs No Statin p=0.24

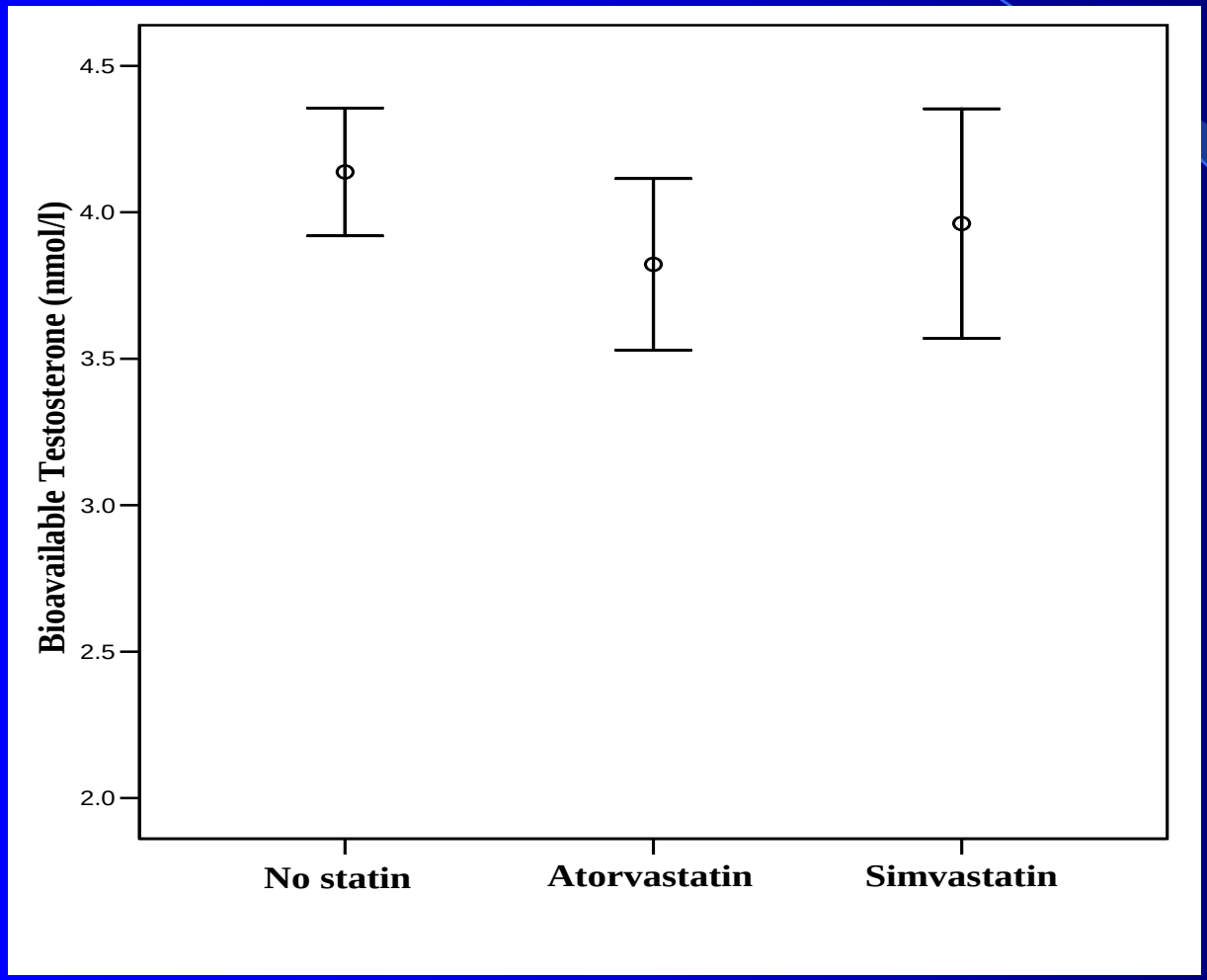
SHBG vs statin use



Atorvastatin vs No Statin p=0.005

Simvastatin vs No Statin p=0.26

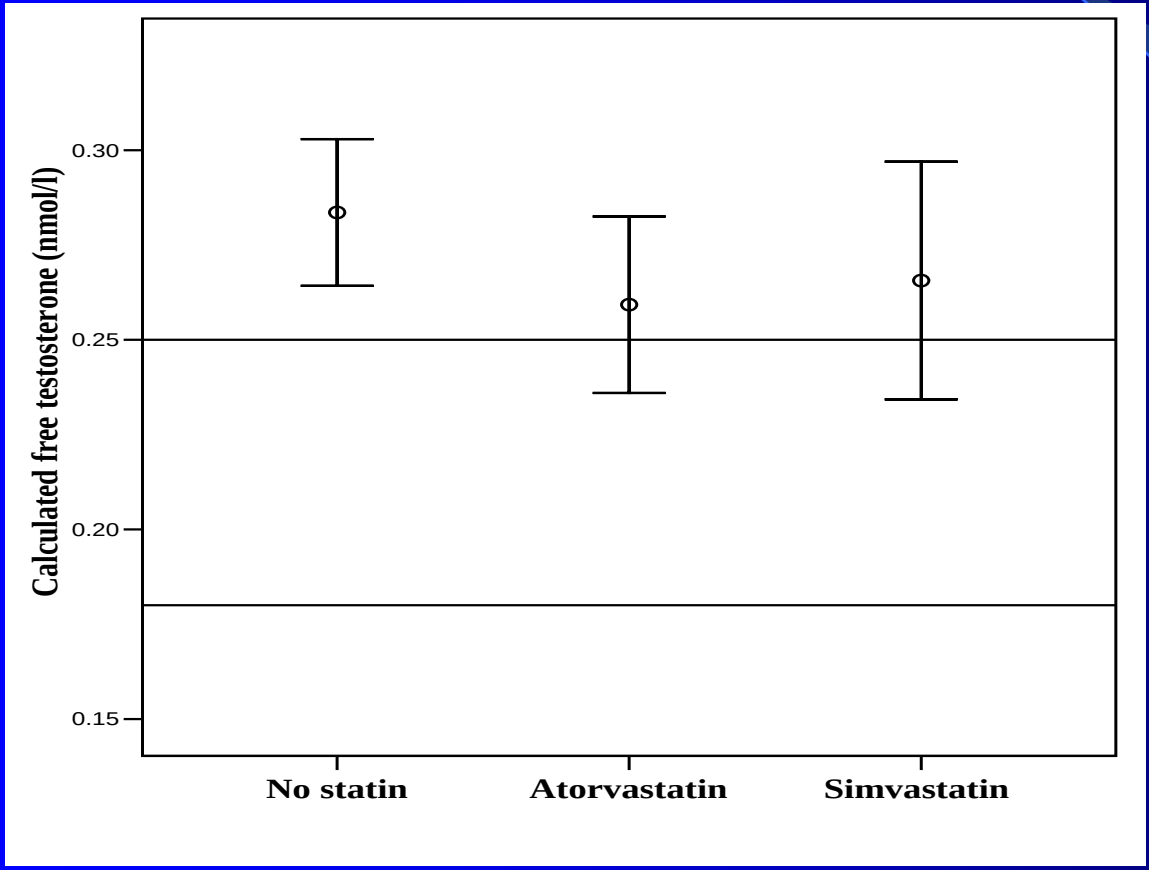
Bioavailable testosterone



Atorvastatin vs
No Statin p=0.10

Simvastatin vs
No Statin p=0.42

Free testosterone



Atorvastatin vs No Statin p=0.148

Simvastatin vs No Statin p=0.344

Other potential benefits of Testosterone in Diabetics with Vascular Disease

- TRT improves cardiac ischaemia and angina symptoms
- TRT improves exercise capacity and improves NYHA class in moderate CHF

(Testosterone acts as a rapid vasodilator at the L-calcium channel blocker)

Conclusion

- Testosterone Replacement Therapy in Hypogonadal men Type 2 Diabetes improves glycaemic control and insulin resistance as well as reducing visceral obesity over 3 months
- What is the mechanism?