

DIABETES, OBESTY AND TESTOSTERONE

Referent

Prof. Thomas Hugh Jones



Transparenzinformation arztCME

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Die Produktneutralität dieser Fortbildung wurde durch ein Review mit zwei Gutachtern geprüft.

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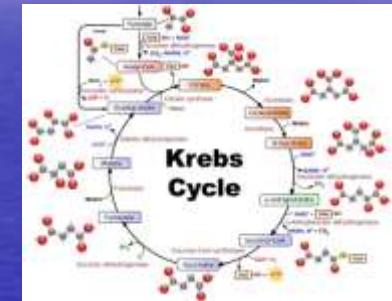
(*) Die Sponsoringbeiträge können je nach Art und Umfang der Fortbildung unterschiedlich sein.

DIABETES, OBESTY AND TESTOSTERONE



T. Hugh Jones

Centre for Diabetes & Endocrinology, Barnsley Hospital
NHS Foundation Trust &
Academic Unit of Diabetes, Endocrinology & Metabolism,
University of Sheffield



Testosterone Deficiency and Mortality in Men with Type 2 Diabetes

N=581

Mean f/u
5.8years

Total Testosterone

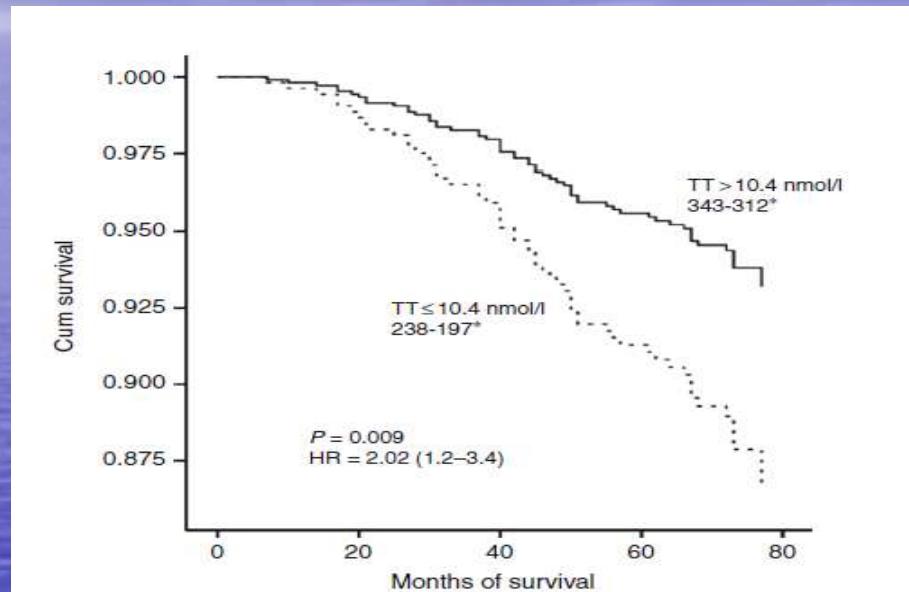


Figure 1 Multivariate-adjusted survival curves using Cox regression model for all-cause mortality based on total testosterone (TT). The solid line represents male subjects with a baseline TT > 10.4 nmol/l and the broken line represents TT ≤ 10.4 nmol/l. HR, hazard ratio for decreased survival after adjusting 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

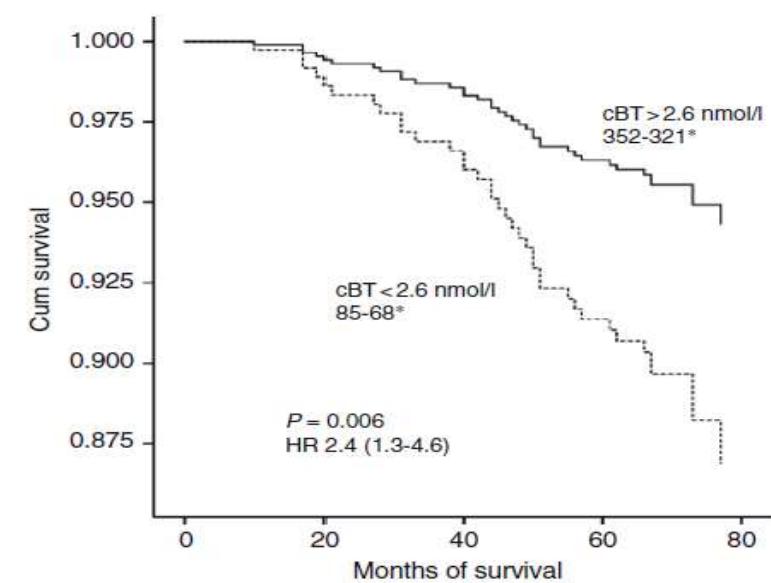


Figure 2 Multivariate-adjusted survival curves using Cox regression model for all-cause mortality based on calculated bioavailable testosterone (cBT). The solid line represents male subjects with a baseline cBT > 2.6 nmol/l and the broken line represents cBT ≤ 2.6 nmol/l. HR, hazard ratio for decreased 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

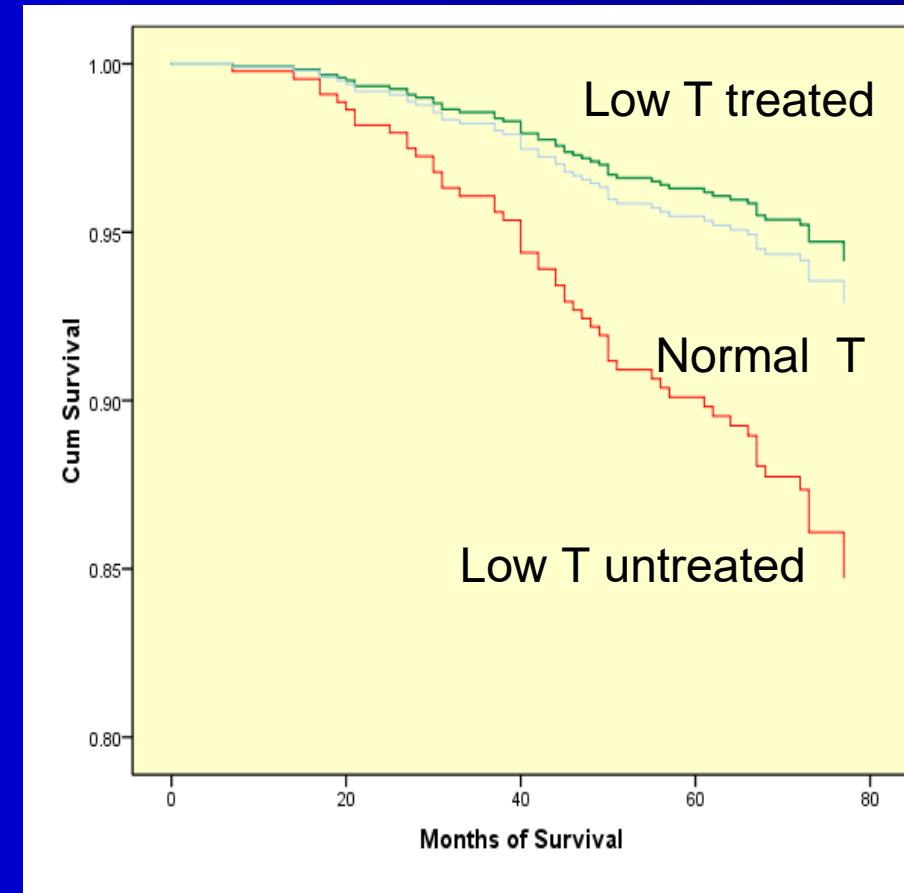
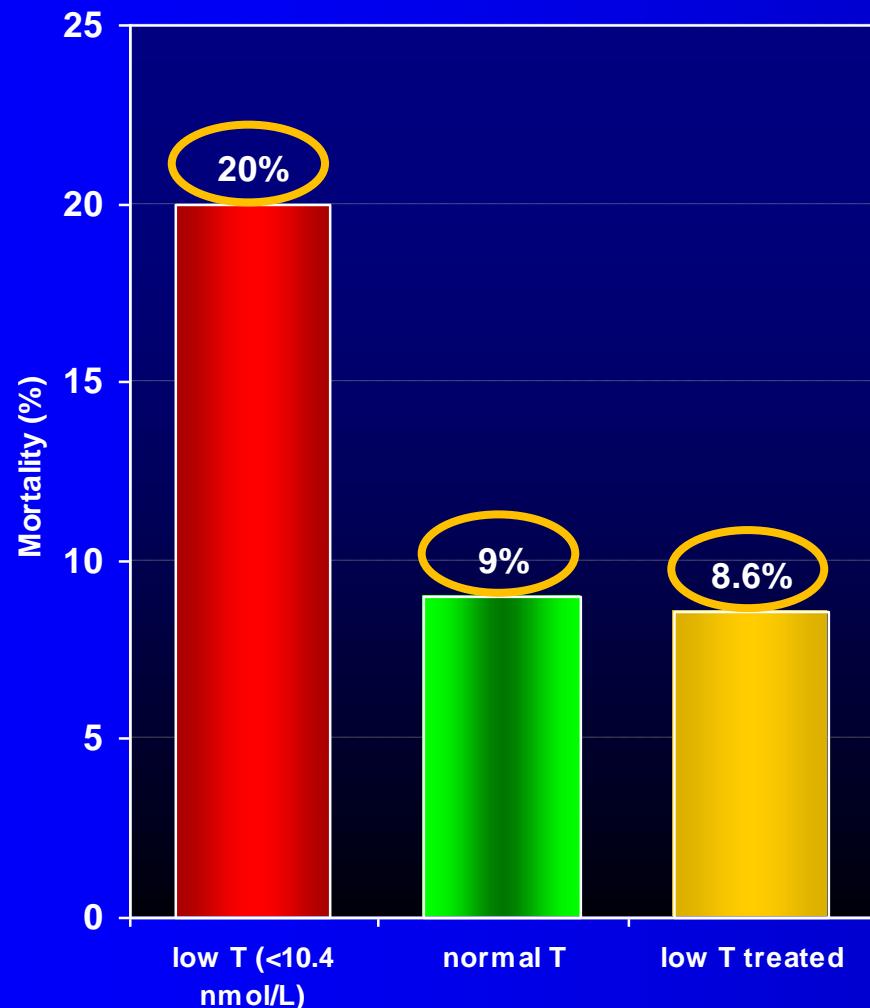
Pre-existing CVD

Cardiovascular Mortality Sub-Analysis

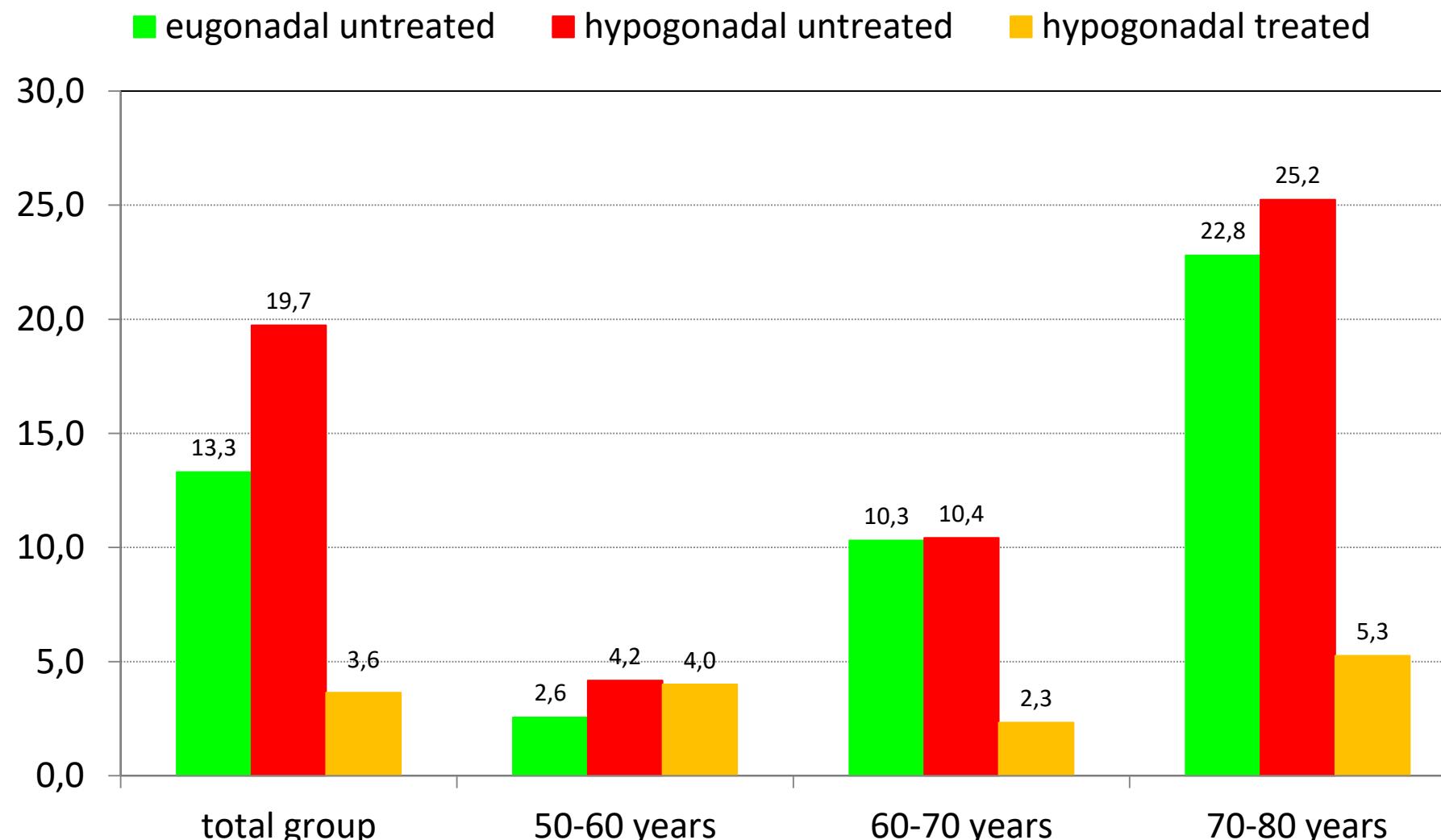
TT<8.4nmol/l HR 2.5 (p=0.02)

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

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

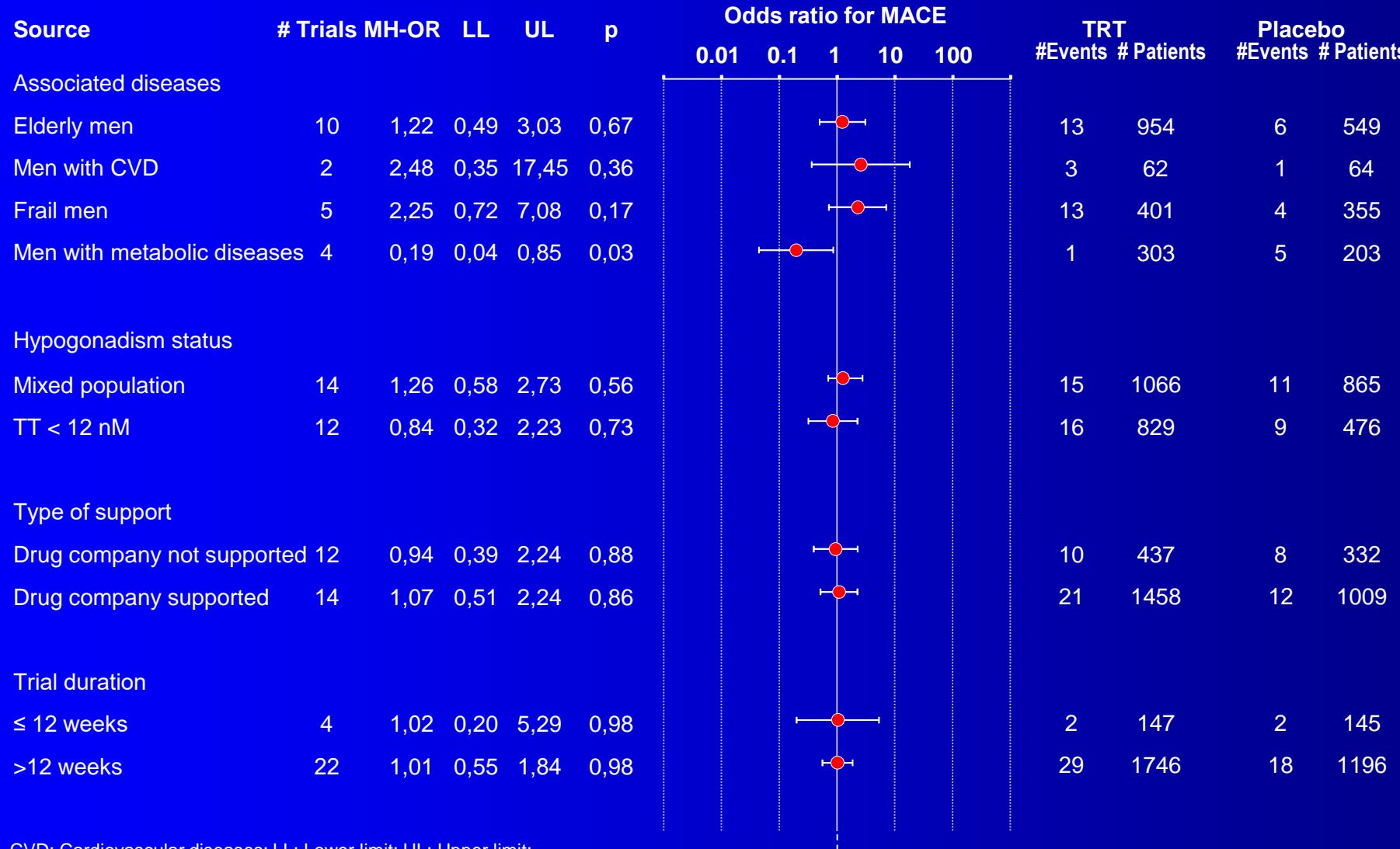


Mortality Data of Patients with Type 2 Diabetes mellitus not Receiving PDE5 Inhibitors Followed for Approximately 4 Years



Odds Ratio for Major Adverse Cardiovascular Events (MACE) According to Baseline Characteristics in Subjects Treated with Testosterone or Placebo

MACE: cardiovascular death, non-fatal myocardial infarction, stroke, acute coronary syndromes, and/or heart failure



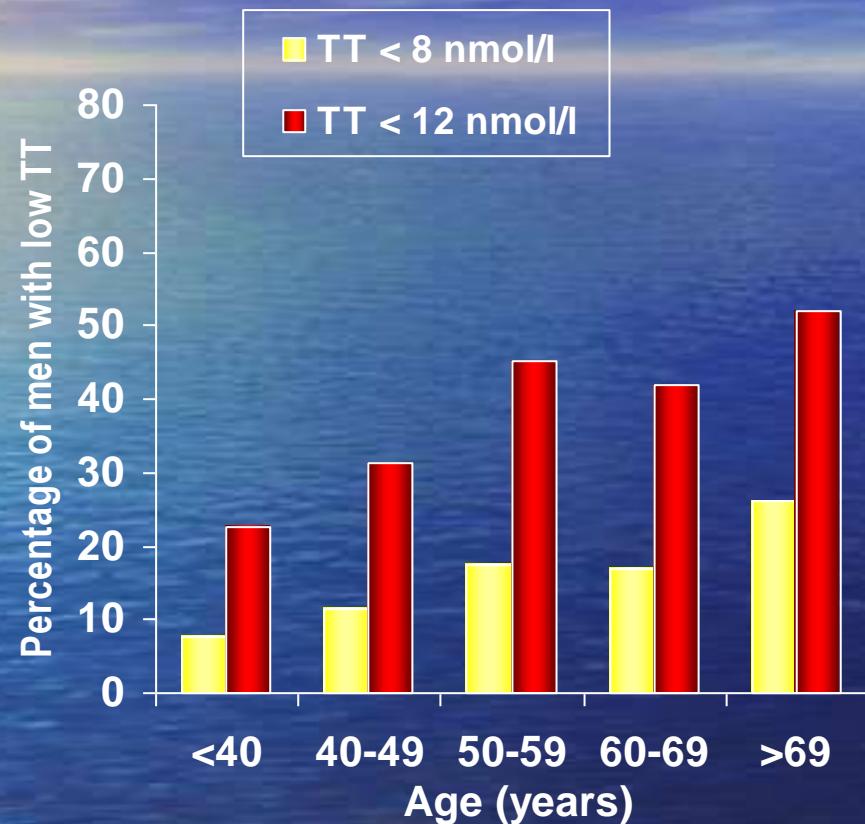
CVD: Cardiovascular diseases; LL: Lower limit; UL: Upper limit;
MH-OR: Mantel-Haenszel odds ratio; TT: Total testosterone

Placebo TS

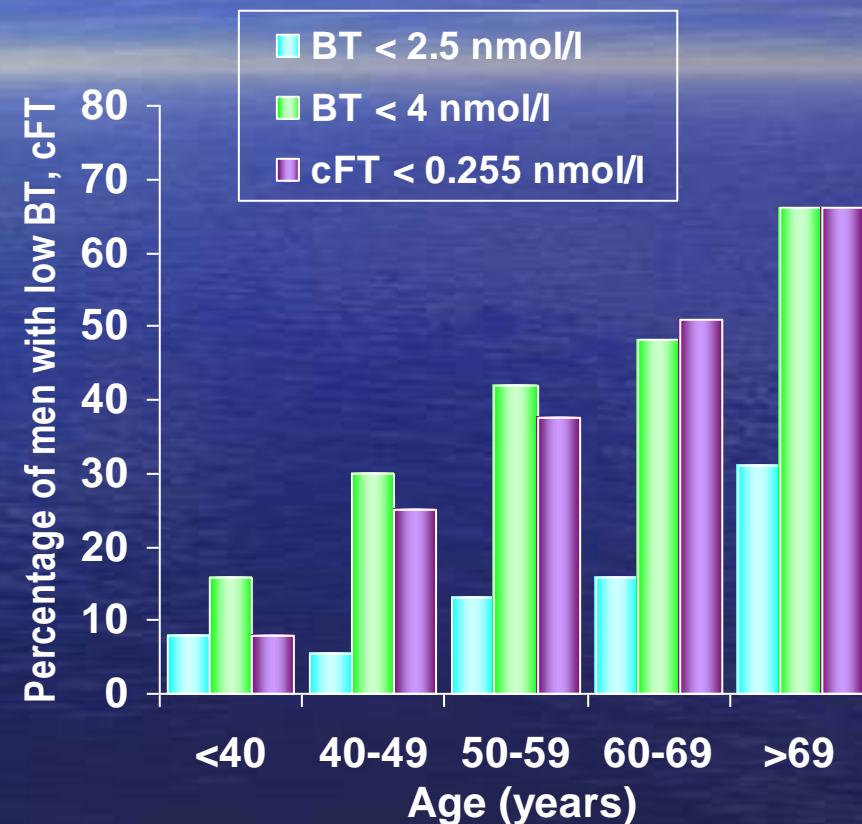
Consequence or Cause?

- Is low testosterone just a biomarker of illness?
- Is it an adaptation to the clinical state?
- Does the low Testosterone state promote disease progression?
- Does Testosterone replacement ameliorate the disease process and improve clinical outcomes?
- Does testosterone replacement improve QOL as well?

Percentage of type 2 diabetic men with positive symptom score with low testosterone by decades of age (ADAM questionnaire)



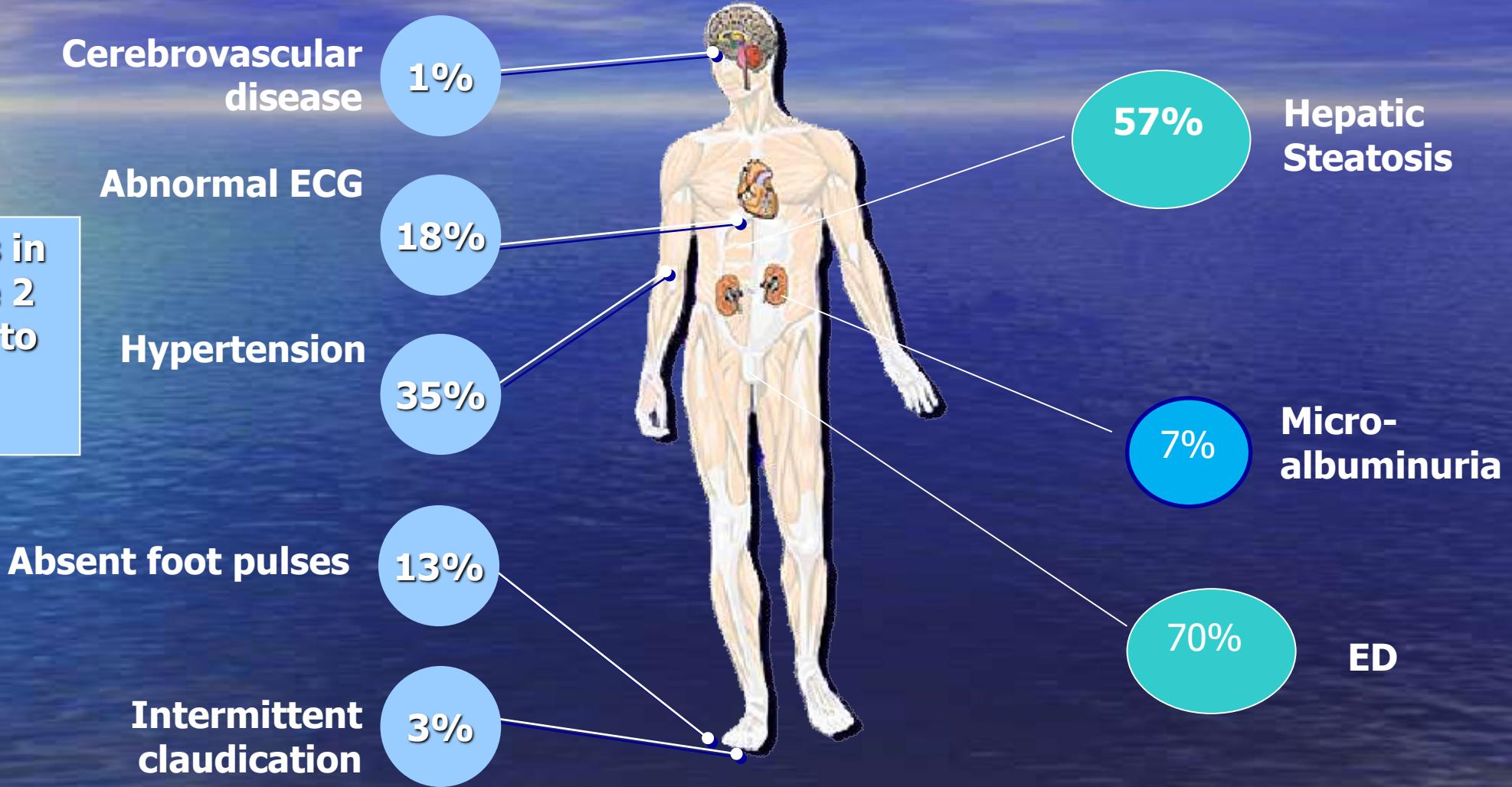
Total testosterone (TT)



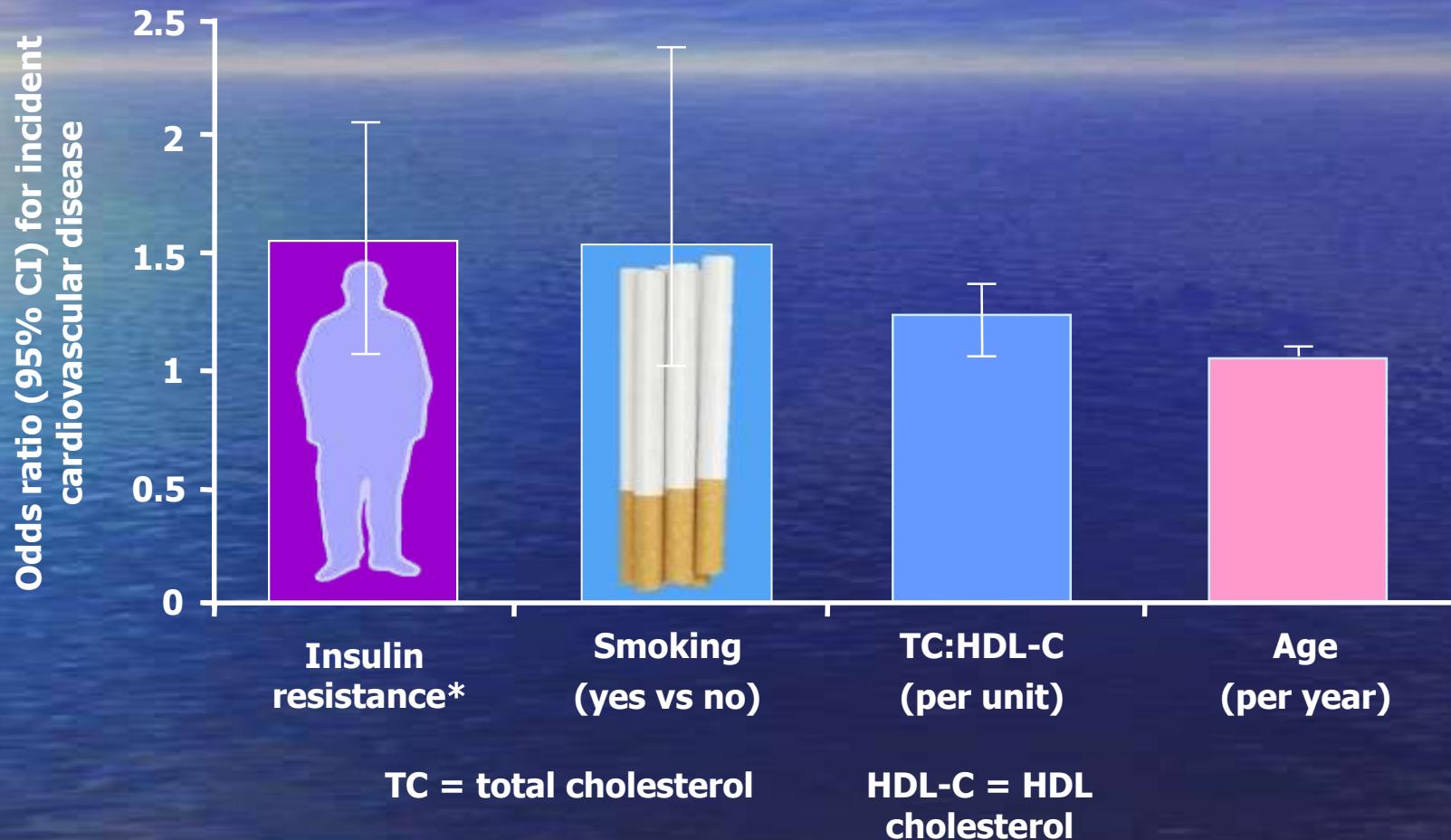
Bioavailable testosterone (BT) and calculated free testosterone (cFT)

Macrovascular disease at diagnosis in Type 2 diabetes

50% of all deaths in people with Type 2 diabetes are due to cardiovascular disease



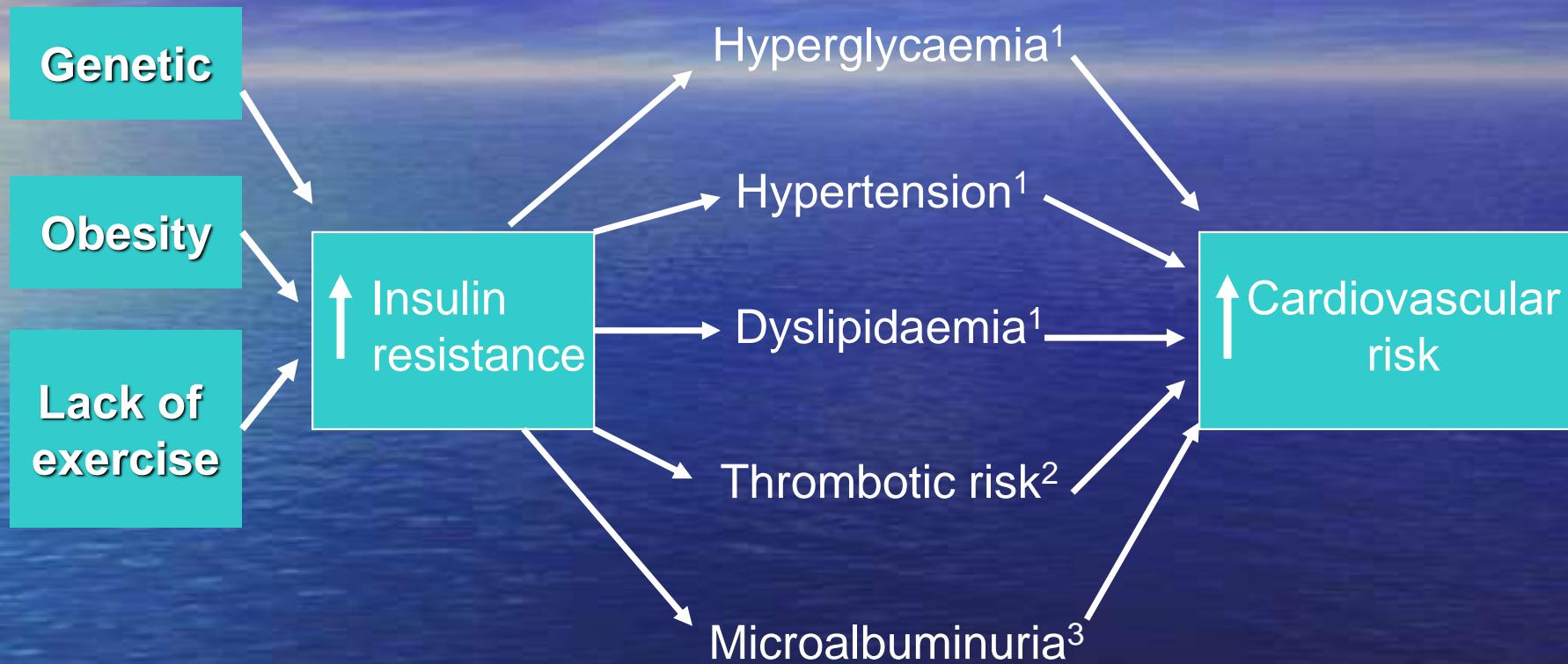
Insulin resistance is an independent predictor of cardiovascular disease



* Measured by log HOMA-IR (per unit)

Bonora E et al. *Diabetes Care* 2002; **25**: 1135–1141.

Insulin resistance syndrome and cardiovascular risk

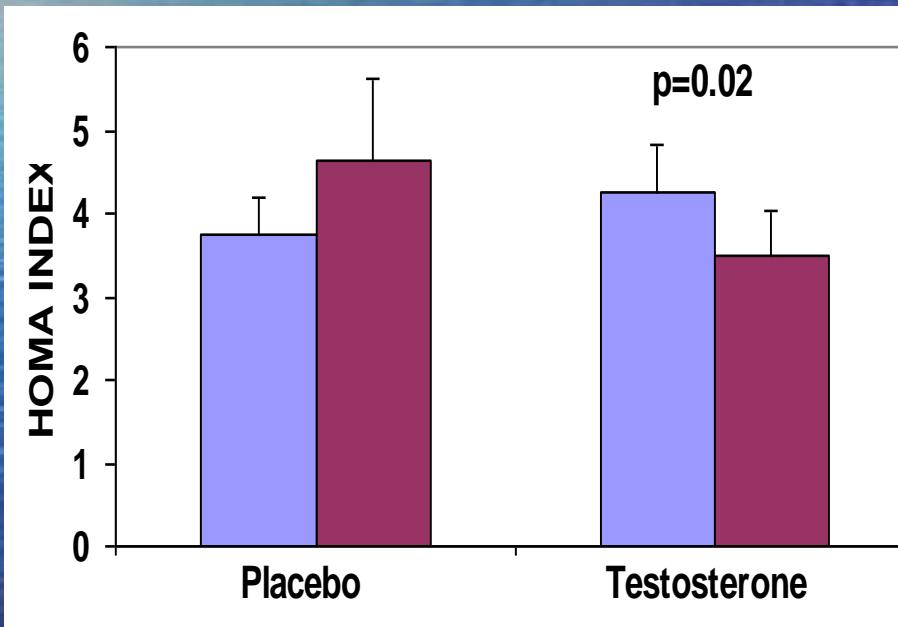


1. Haffner SM, Miettinen H. Am J Med 1997; 103: 152–62.

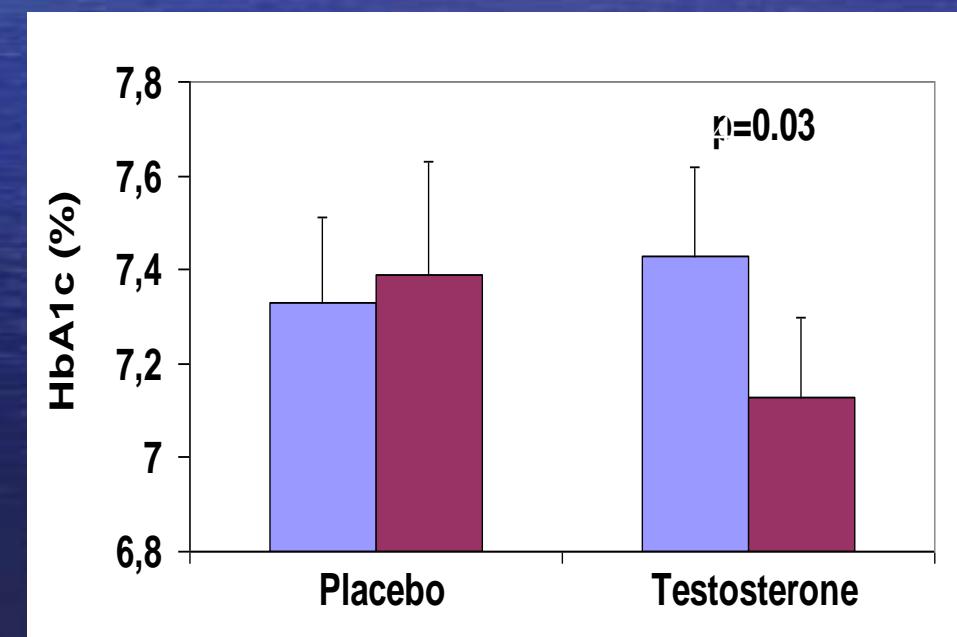
2. Reaven GM. J Int Med 1994; 236: (Suppl 736): 13–22.

3. Abuaisla B. Diabet Res Clin Pract 1998; 39: 93–99.

CLINICAL STUDY

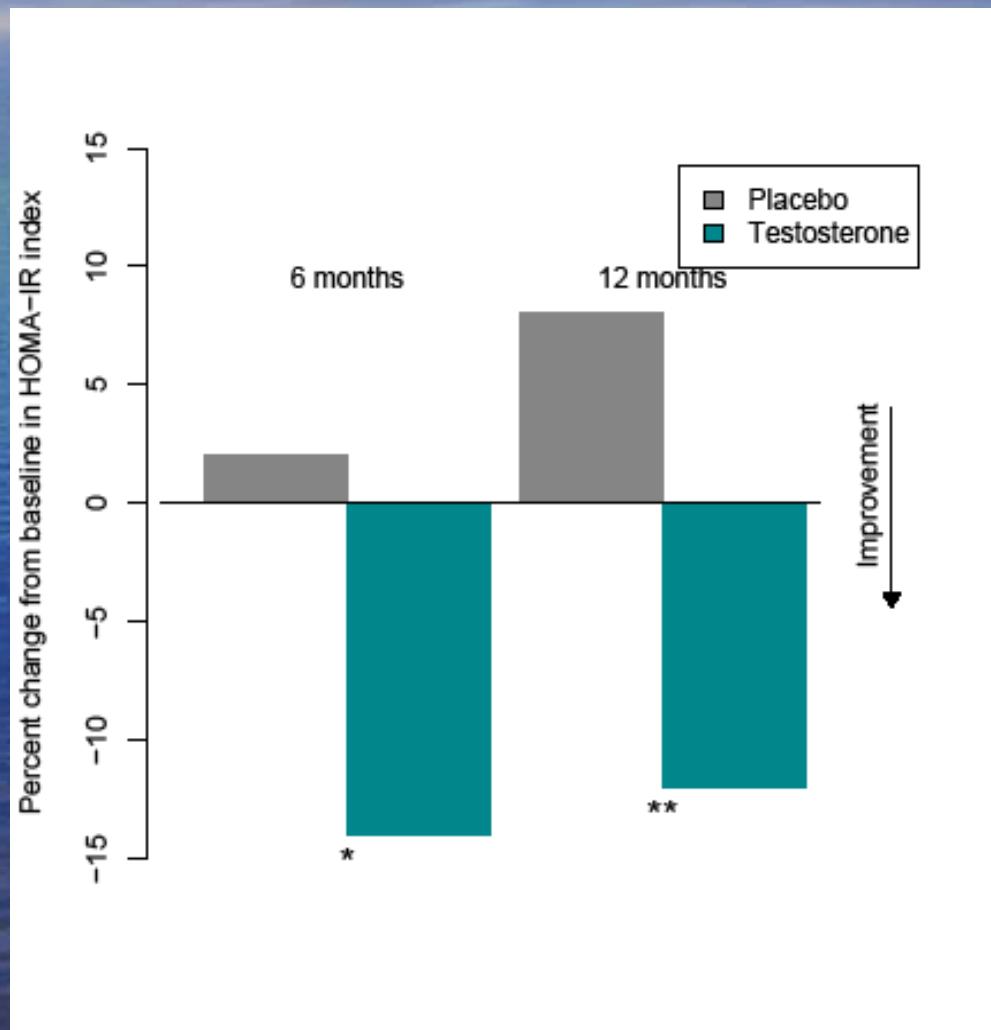
Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetesD Kapoor^{1,3}, E Goodwin¹, K S Channer² and T H Jones^{1,3}¹Centre for Diabetes and Endocrinology, Barnsley NHS Foundation Trust Hospital, Gawber Road, Barnsley S75 2EP, UK, ²Department of Cardiology, Royal Hallamshire Hospital, Sheffield, UK and ³Academic Unit of Endocrinology, Division of Genomic Medicine, University of Sheffield, UK(Correspondence should be addressed to T H Jones; Email: hugh.jones@bath-tr.trent.nhs.uk)

n=14



n=24

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



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

EFFECT of TRT on HOMA-ir and HbA1c

In Hyogonadal Men with the Metabolic Syndrome and/or Type 2 Diabetes over 12 months (n=220)

TIMES2 Study

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

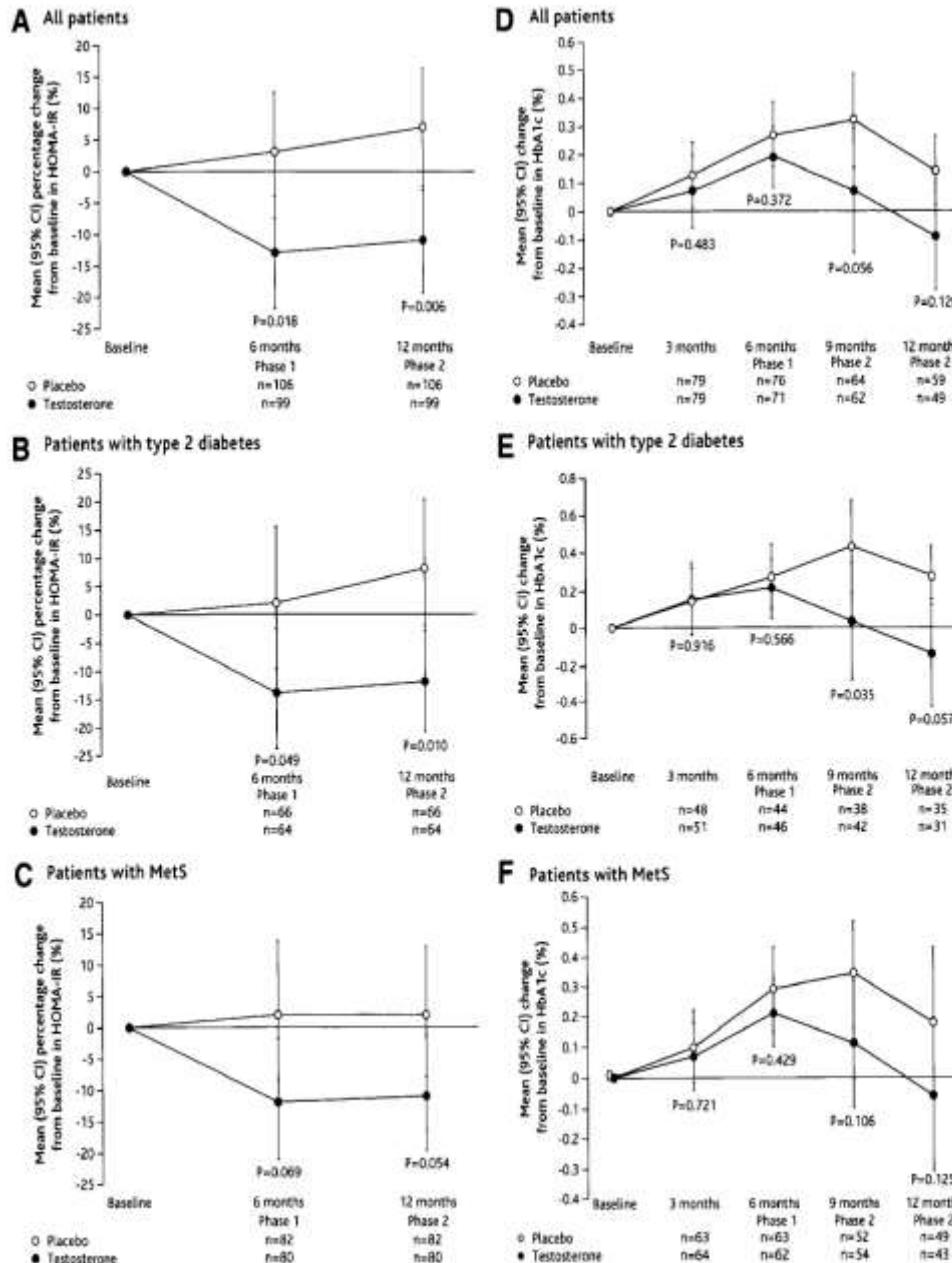
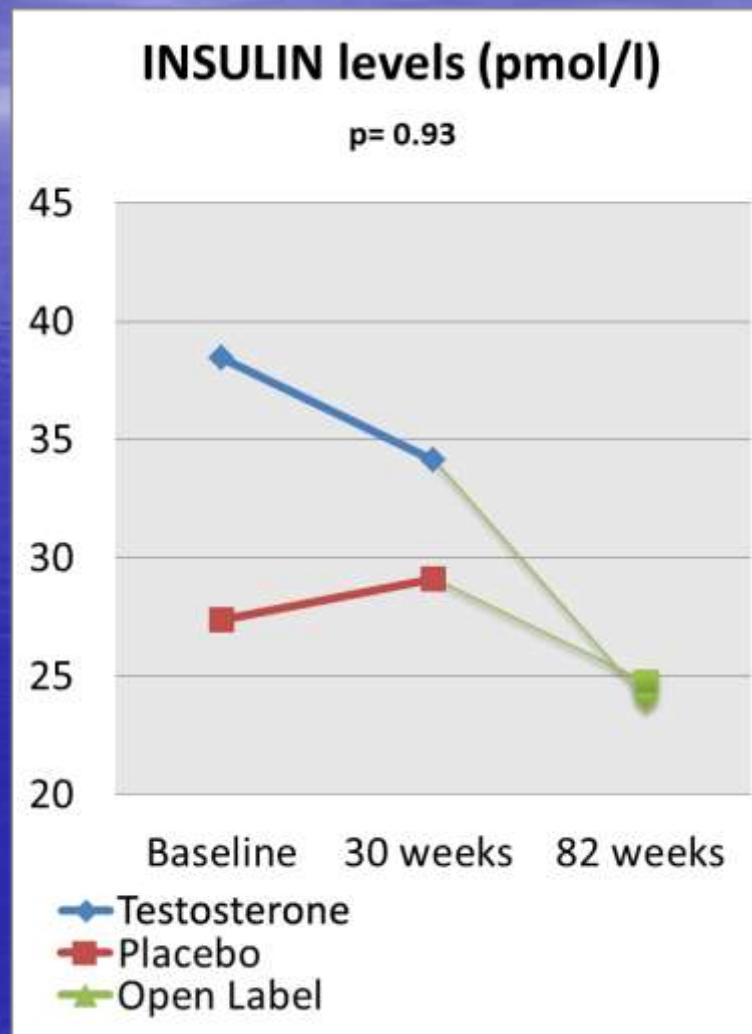
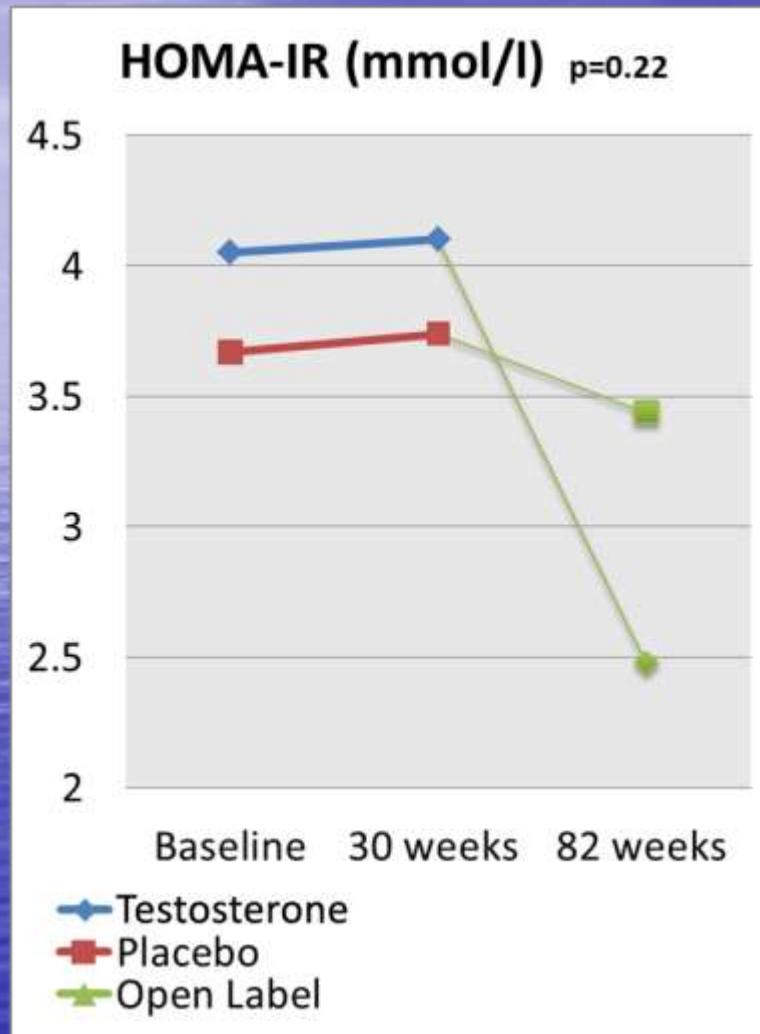


Figure 1—Mean (95% CI) percentage change from baseline in HOMA-IR (ITT population, last observation carried forward) and change from baseline in HbA_{1c} (ITT population, study completers) among all patients (A and D), patients with type 2 diabetes (B and E), and patients with MetS (C and F). P values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

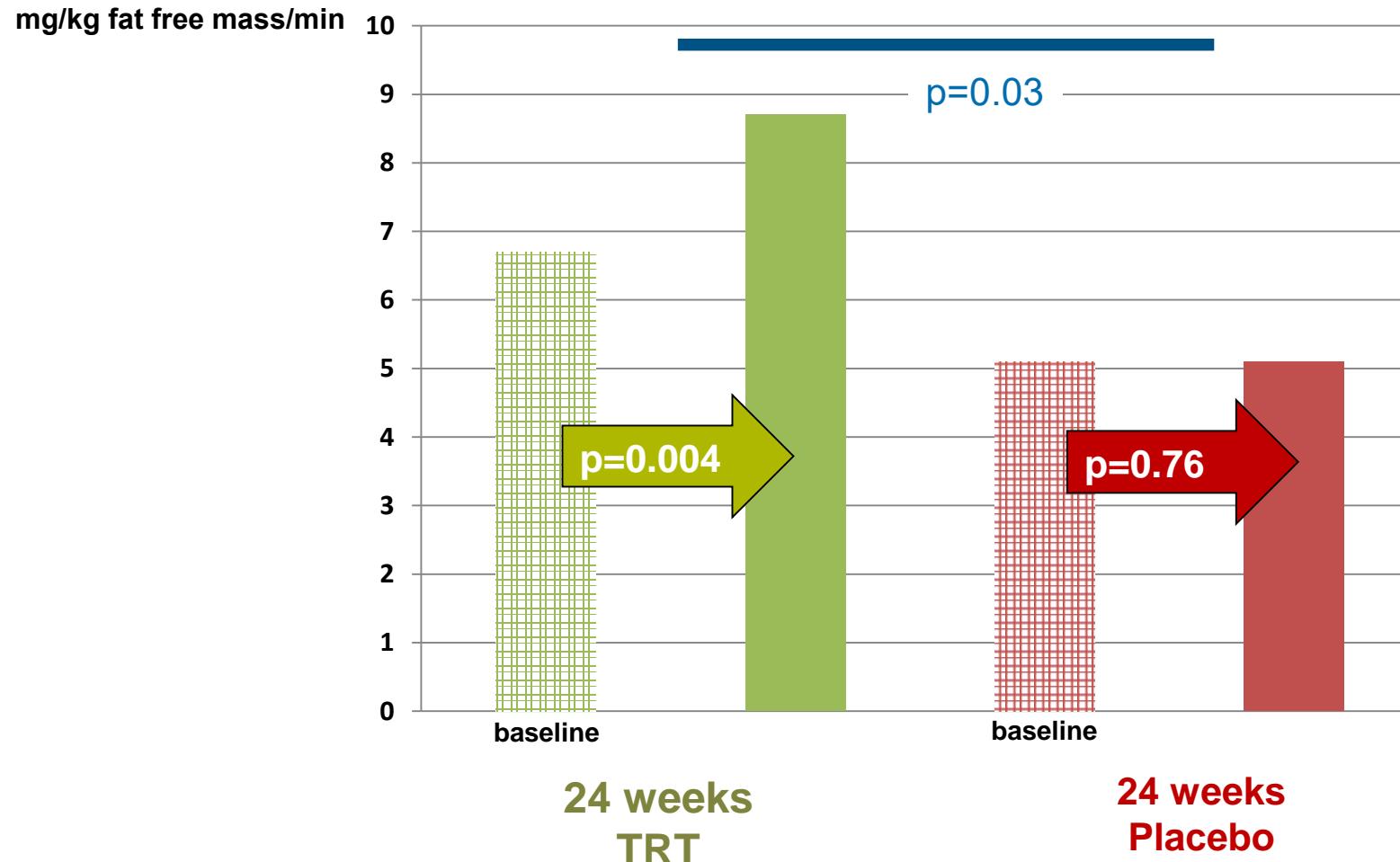
HOMA-IR and Serum INSULIN



Hackett G et al. J Sex Med
2014;11:840-56

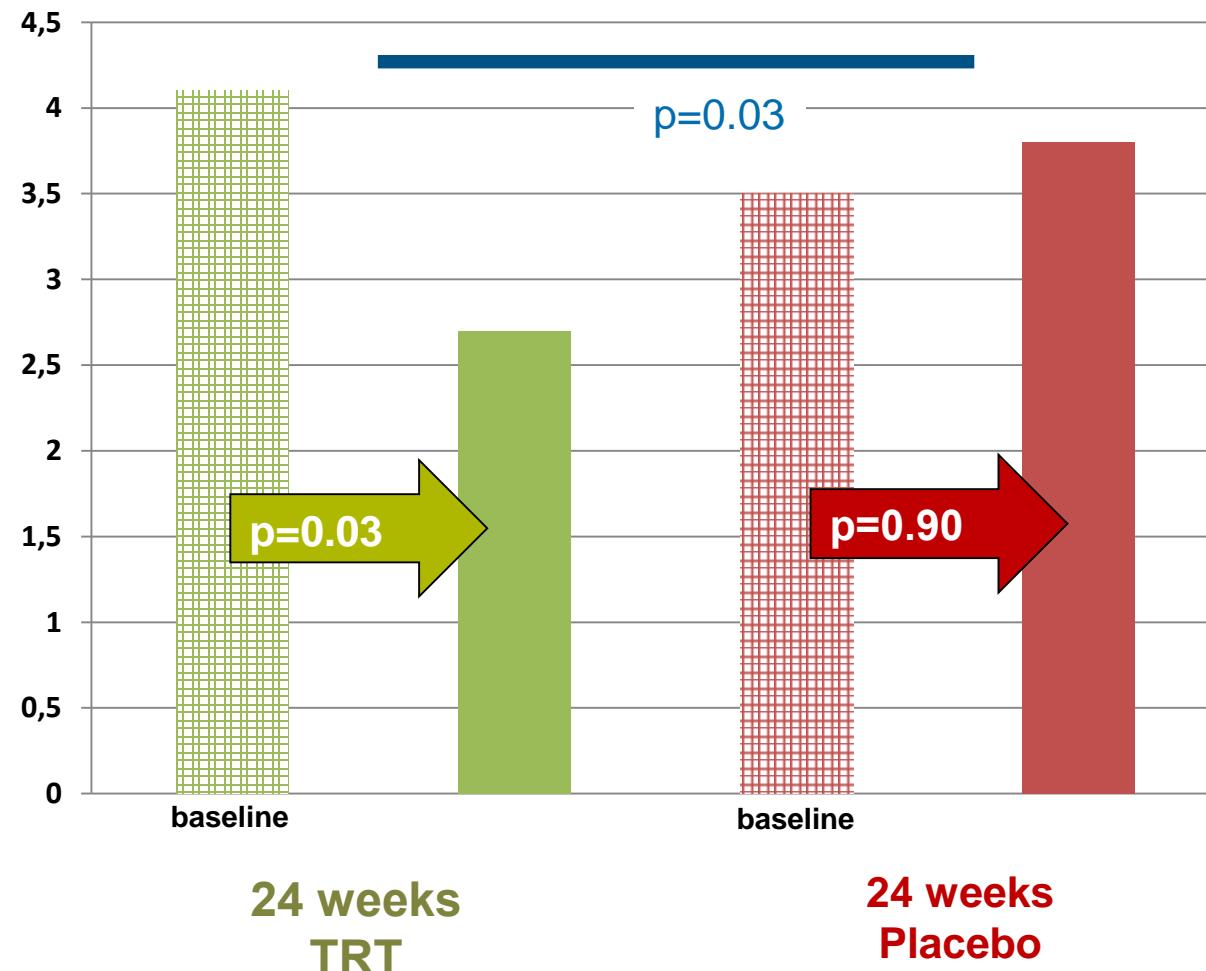
Insulin Sensitivity

Clamp Trial - Glucose Infusion Rate (GIR)



Insulin Resistance

HOMA-IR



Testosterone Therapy Increases Lean Body Mass and Reduces Total Body Fat Mass in Men with Testosterone Deficiency

Study	Testosterone formulation	Treatment period	Lean body mass	Fat mass
Marin et al. [27]	Gel	9 months	↑	↓
Snyder et al. [28]	Patch	36 months	↑	↓
Kenny et al. [29]	Patch	12 months	↑	↓
Crawford et al. [30]	Mixed esters	12 months	↑	↓
Ferrando et al. [31]	TE	6 months	↑	↓
Steidle et al. [32]	Gel	3 months	↑	↓
Wittert et al. [33]	Oral TU	12 months	↑	↓
Casaburi et al. [34]	TE	3 months	↑	↓
Page et al. [35]	TE	36 months	↑	↓
Kapoor et al. [20]	Mixed esters	3 months	↑	↓
Bhasin et al. [36]	TE	5 months	↑	↓
Kapoor et al. [37]	Mixed esters	3 months	↑	↓
Bhasin et al. [38]	Gel	6 months	↑	↓
Svartberg et al. [39]	Injectable TU	12 months	↑	↓
Allan et al. [40]	Patch	12 months	↑	↓
Srinivas-Shankar et al. [41]	Gel	6 months	↑	↓
Aversa et al. [42]	Injectable TU	24 months	↑	↓
Aversa et al. [43]	Injectable TU	12 months	↑	↓
Behre et al. [44]	Gel	6 months	↑	↓
Finkelstein et al. [45*]	Gel	4 months	↑	↓
Francomano et al. [46**]	Injectable TU	60 months	↑	↓
Bouloux et al. [47]	Oral TU	12 months	↑	↓
Pexman-Fieth et al. [48]	Gel	6 months	↑	↓
Juang et al. [49]	Gel	3 months	↑	↓
Rodriguez-Tolra et al. [50]	Gel/Injectable TU	24 months	↑	↓
Frederiksen et al. [51]	Gel	6 months	↑	↓
Emmelot-Vonk et al. [52]	Oral TU	6 months	↑	↓
Borst et al. [53]	TE	12 months	↑	↓

TE, testosterone enanthate; TU, testosterone undecanoate

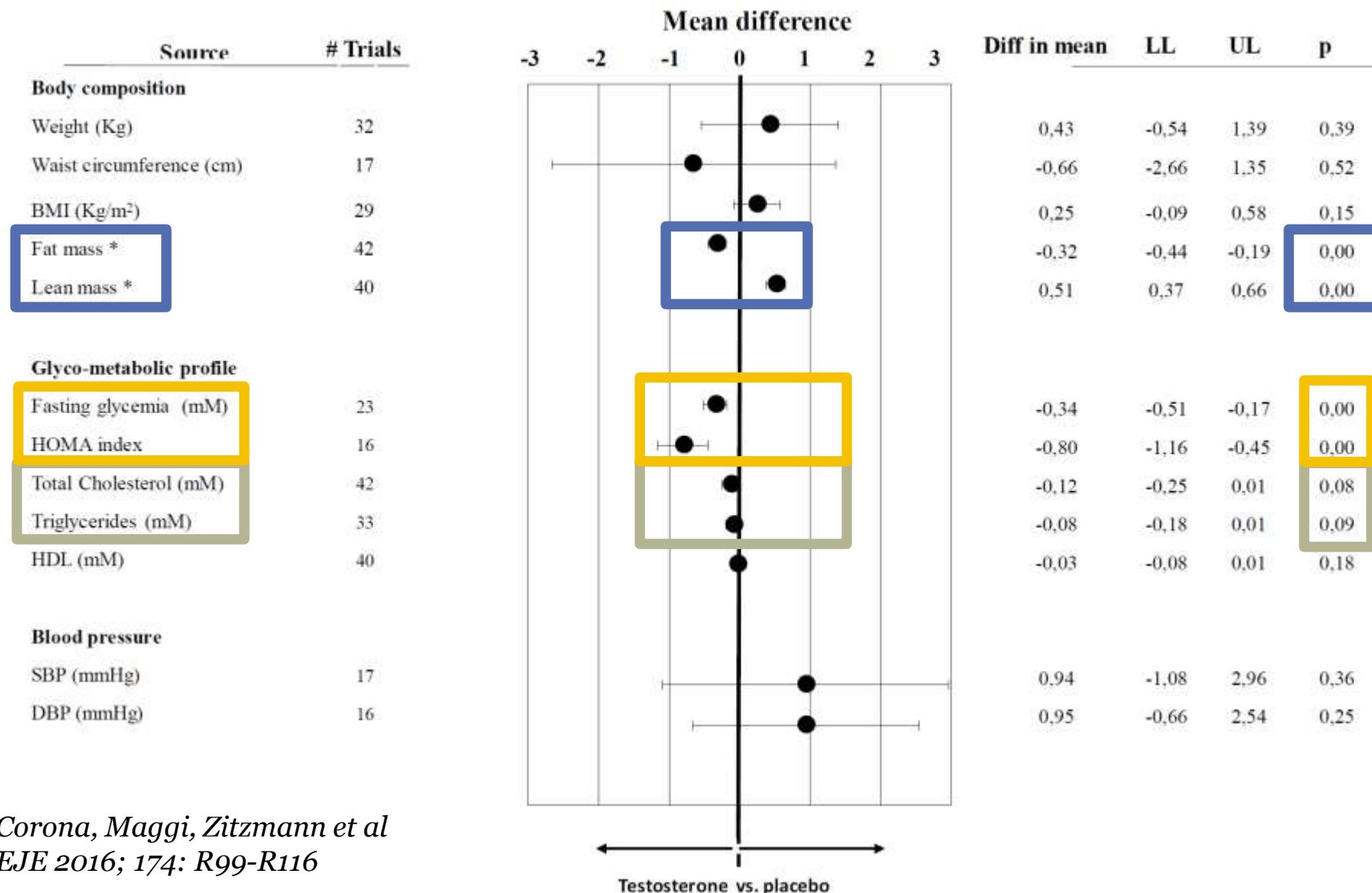
Effects of Testosterone Therapy on Weight, Waist Circumference and BMI

Study	Testosterone formulation	Treatment period	Weight	Waist circumference	Body mass index
Marin et al. [27]	Gel	9 months	ND	↓	ND
Kapoor et al. [20,37]	Mixed esters	3 months	ND	↓	ND
Svartberg et al. [39]	Injectable TU	12 months	ND	↓	ND
Heufelder et al. [54]	Gel	12 months	ND	↓	ND
Aversa et al. [42]	Injectable TU	24 months	ND	↓	ND
Aversa et al. [43]	Injectable TU	12 months	ND	↓	ND
Kalinchenko et al. [55]	Injectable TU	7 months	↓	↓	↓
Aversa et al. [56]	Injectable TU	36 months	ND	↓	ND
Zitzmann et al. [57*]	Injectable TU	9–12 months	ND	↓	ND
Francomano et al. [46**]	Injectable TU	60 months	↓	↓	↓
Francomano et al. [58**]	Injectable TU	12 months	↓	↓	↓
Haider et al. [59**]	Injectable TU	12–72 months	↓	↓	↓
Haider et al. [60**]	Injectable TU	12–72 months	↓	↓	↓
Saad et al. [23**]	Injectable TU	12–60 months	↓	↓	↓
Yassin and Doros [61**]	Injectable TU	12–60 months	↓	↓	↓
Pexman-Fieth et al. [48]	Gel	6 months	↓	↓	↓
Hackett et al. [62*,63*]	Injectable TU	7 and 20 months	↓	↓	↓
Bhattacharya et al. [64,65]	Gel	12 months	ND	↓	ND
Garcia et al. [66]	Injectable TU	24 months	ND	↓	ND
Zitzmann et al. [72]	Injectable TU	12–192 months	↓	↓	↓

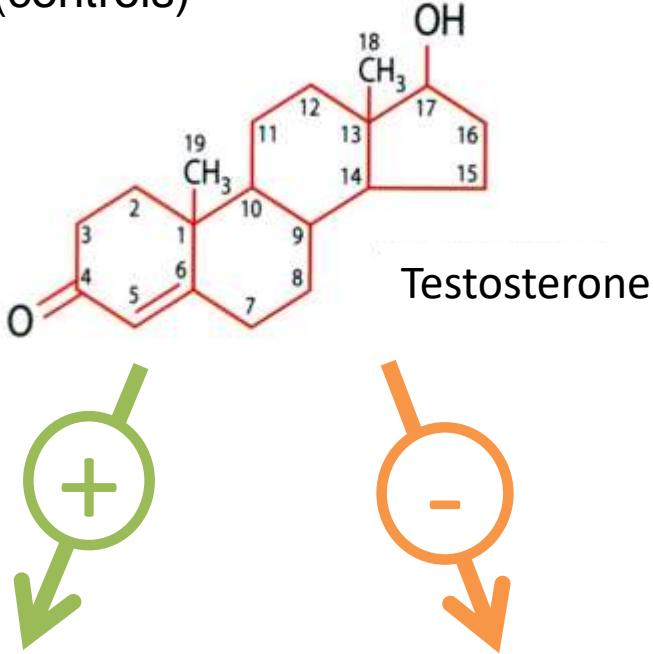
ND, no data; TU, testosterone undecanoate

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

3029 men (treated) vs 2049 (controls)

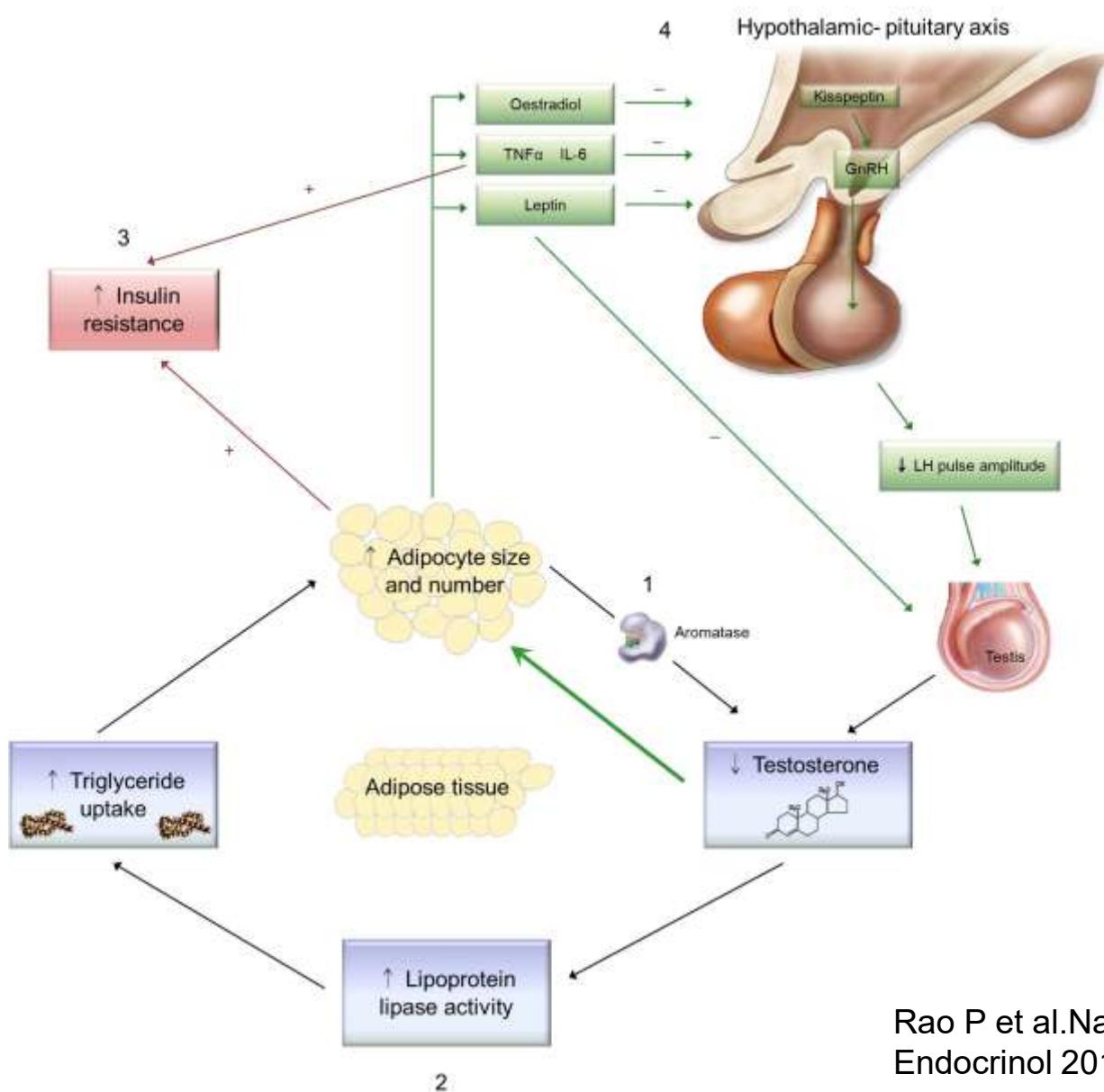


**Meta-Analysis of 59 randomized controlled trials of
T substitution in hypogonadism**
3029 men (treated) vs 2049 (controls)



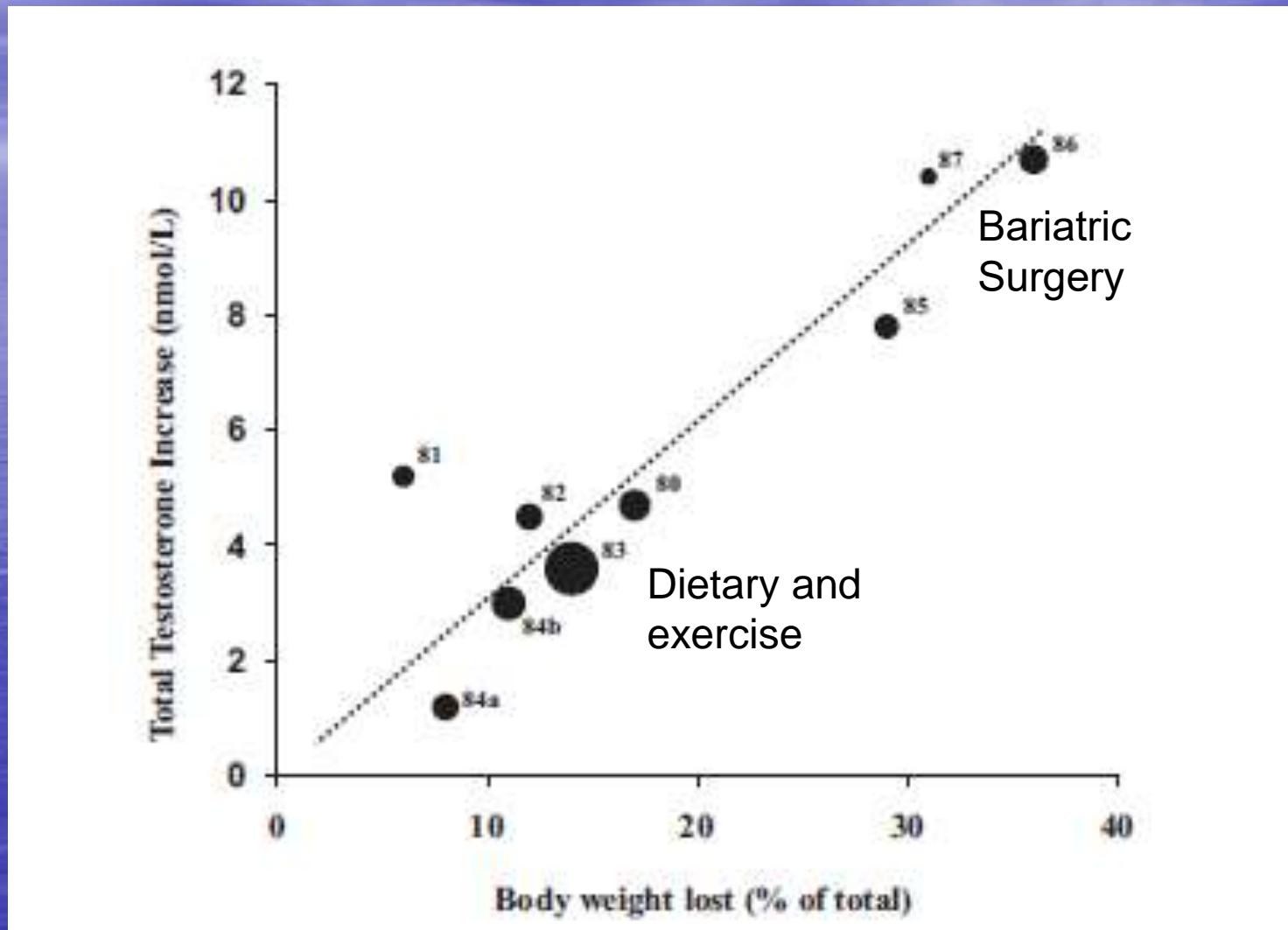
	Lean mass		Fat mass	
	Adj r	p	Adj r	p
HOMA index	0.82	0.001	-0.02	0.43
Fasting glycemia	0.48	0.001	-0.05	0.27

HYPOGONADAL-OBESITY-ADIPOCYTOKINE HYPOTHESIS

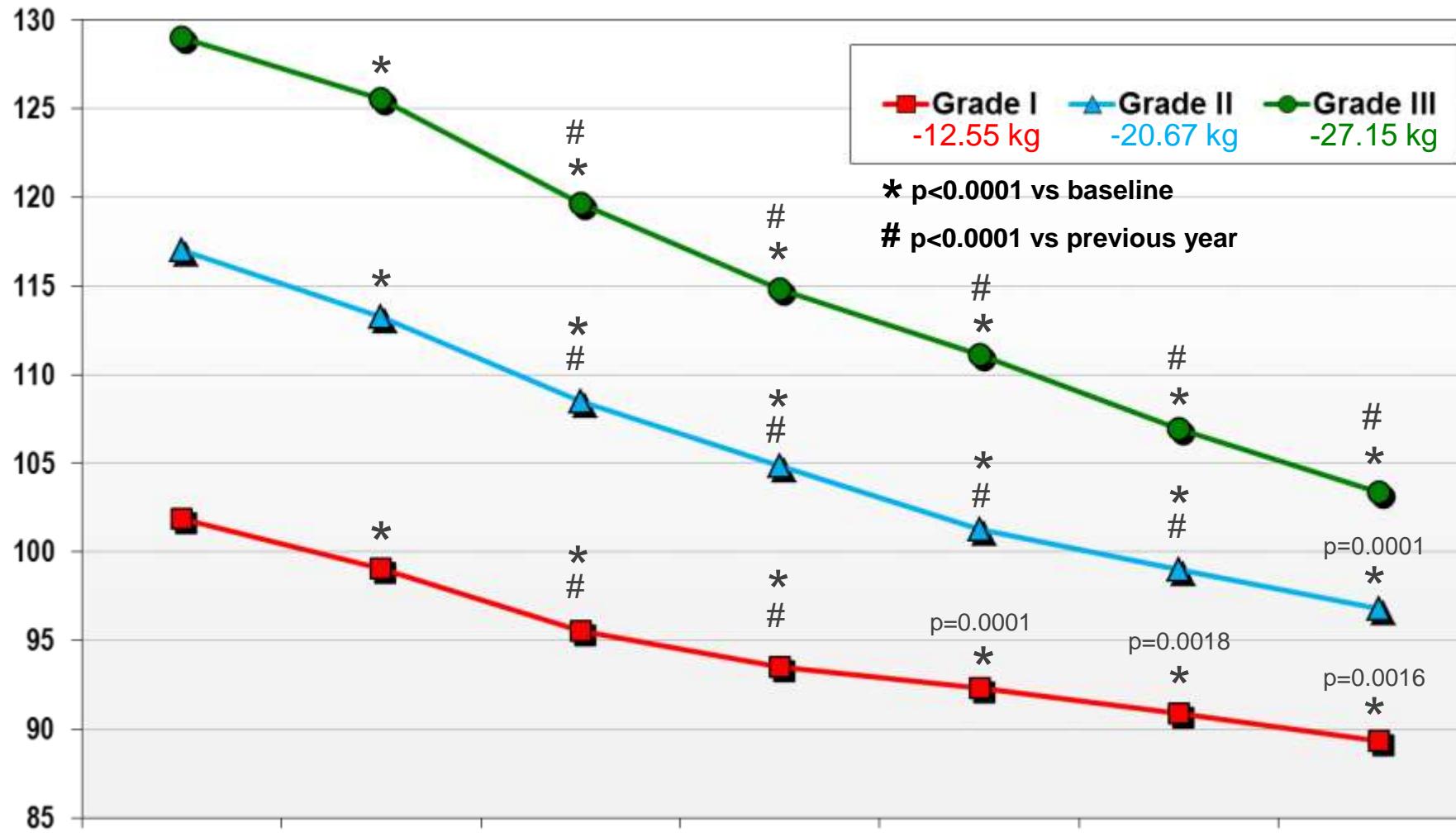


Rao P et al. Nature Reviews Endocrinol 2013;9:479-493

Effect of Weight Loss on Testosterone Levels



Weight (kg) in 362 Hypogonadal Men with Different Grades of Obesity Receiving Long-Term Treatment with Testosterone Undecanoate Injections



NI= 185

NII= 131

NIII= 46

177

124

44

169

125

46

159

121

43

141

104

37

126

90

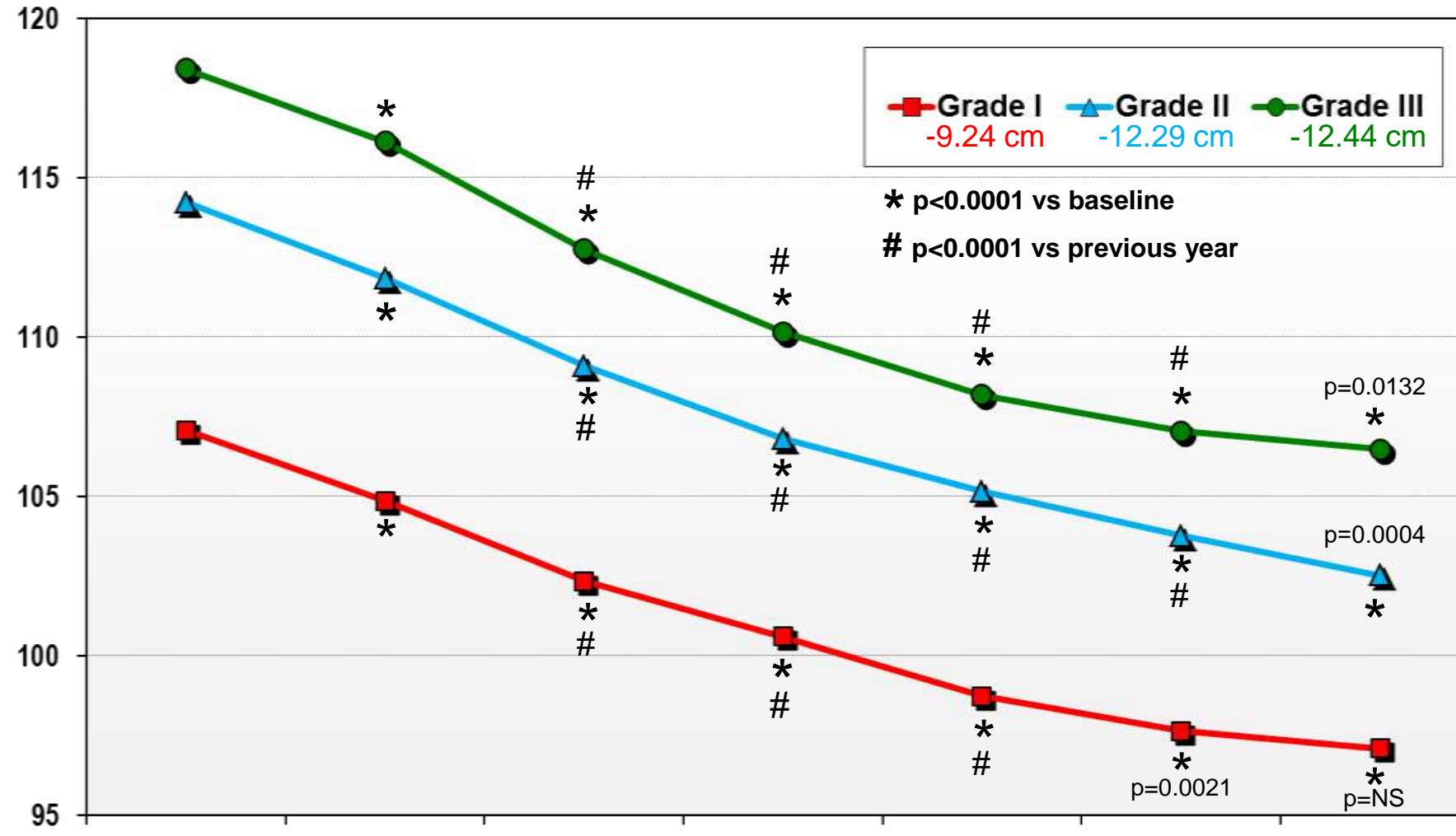
34

84

64

24

**Waist Circumference (cm) in 362 Hypogonadal Men with Different Grades of Obesity
Receiving Long-Term Treatment with Testosterone Undecanoate Injections**



NI = 185

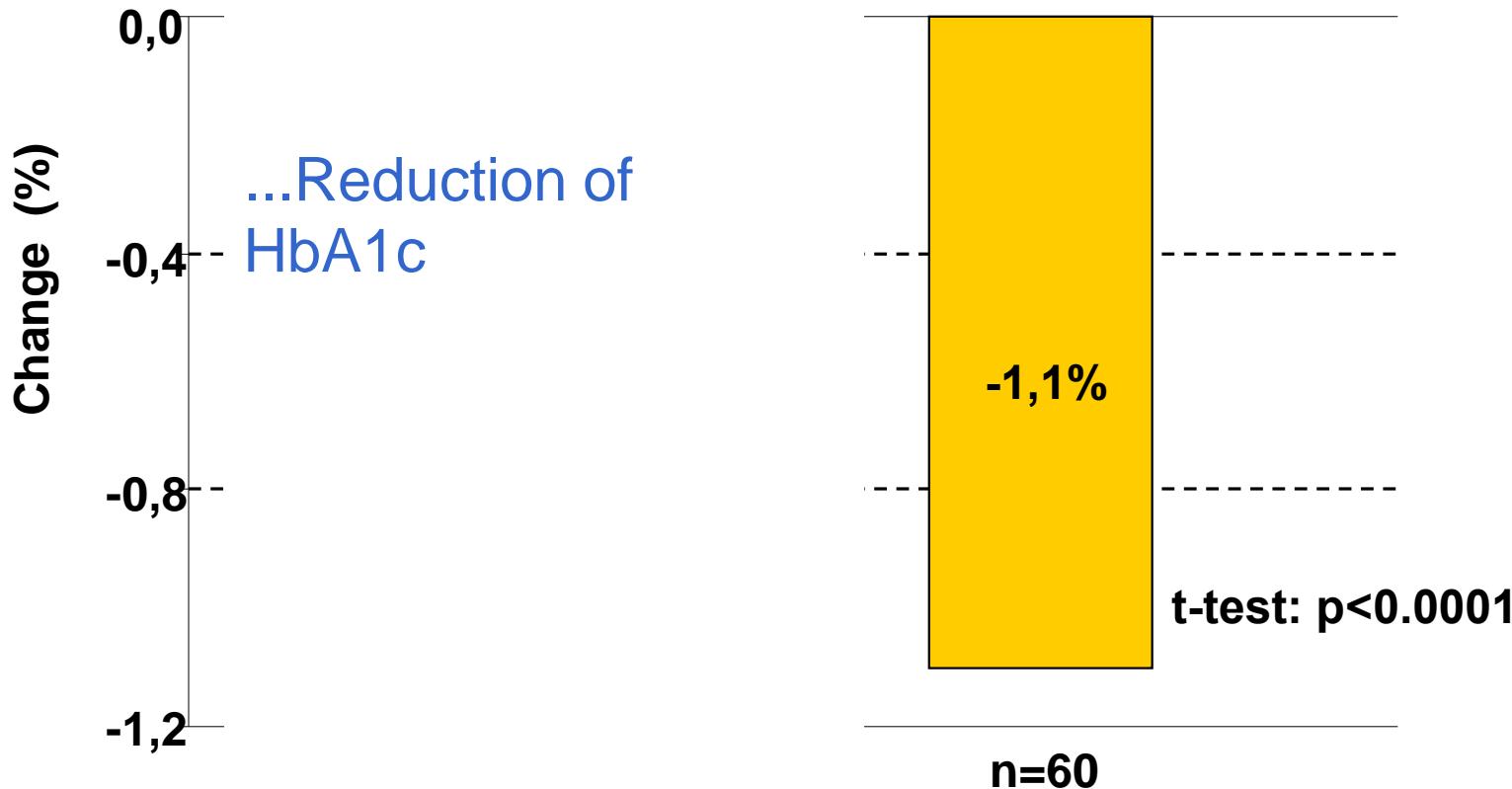
NII = 131

NIII = 46

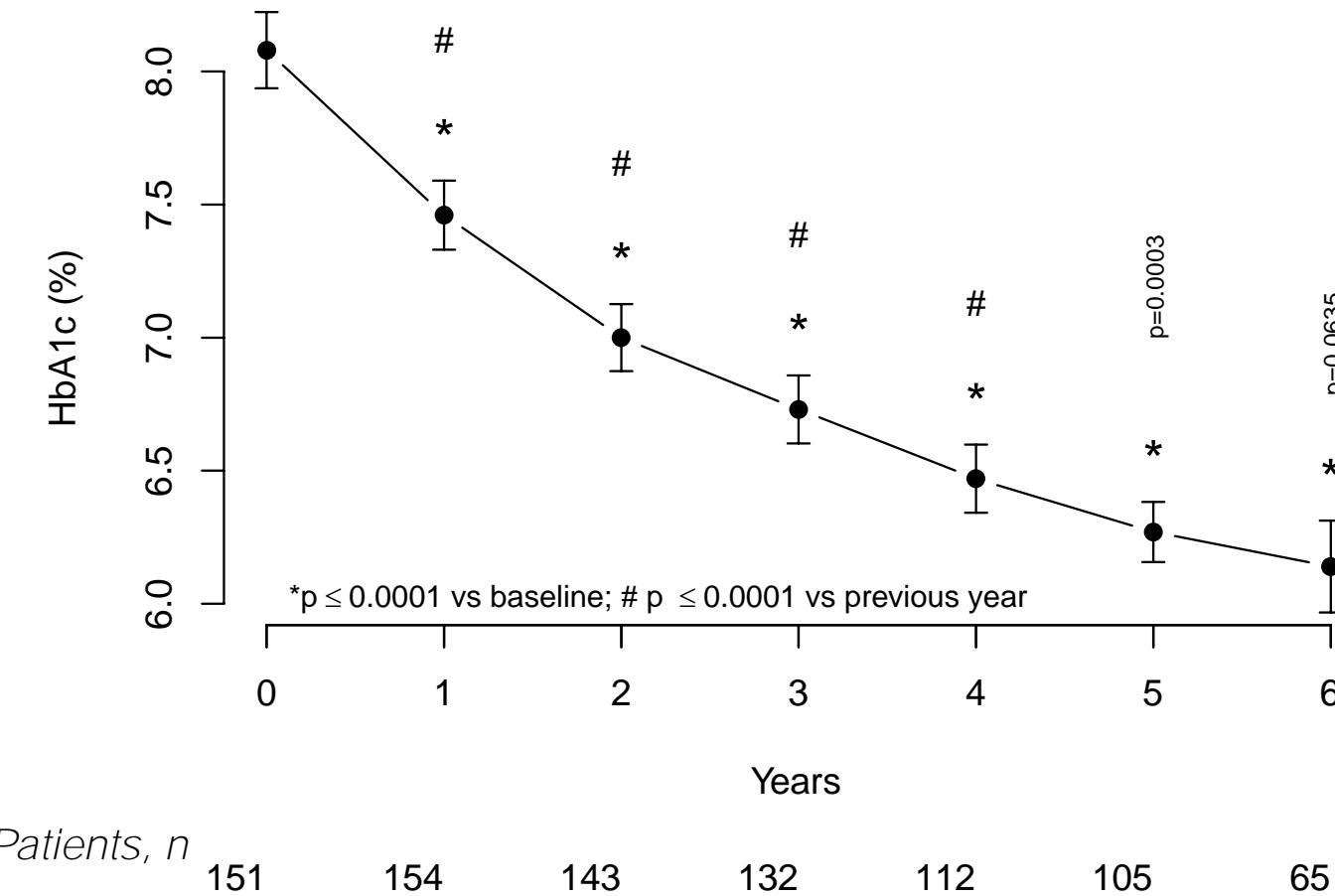
IPASS: intramuscular testosterone undecanoate in hypogonadal Men with Type 2 Diabetes mellitus

Treatment of symptomatic hypogonadal men

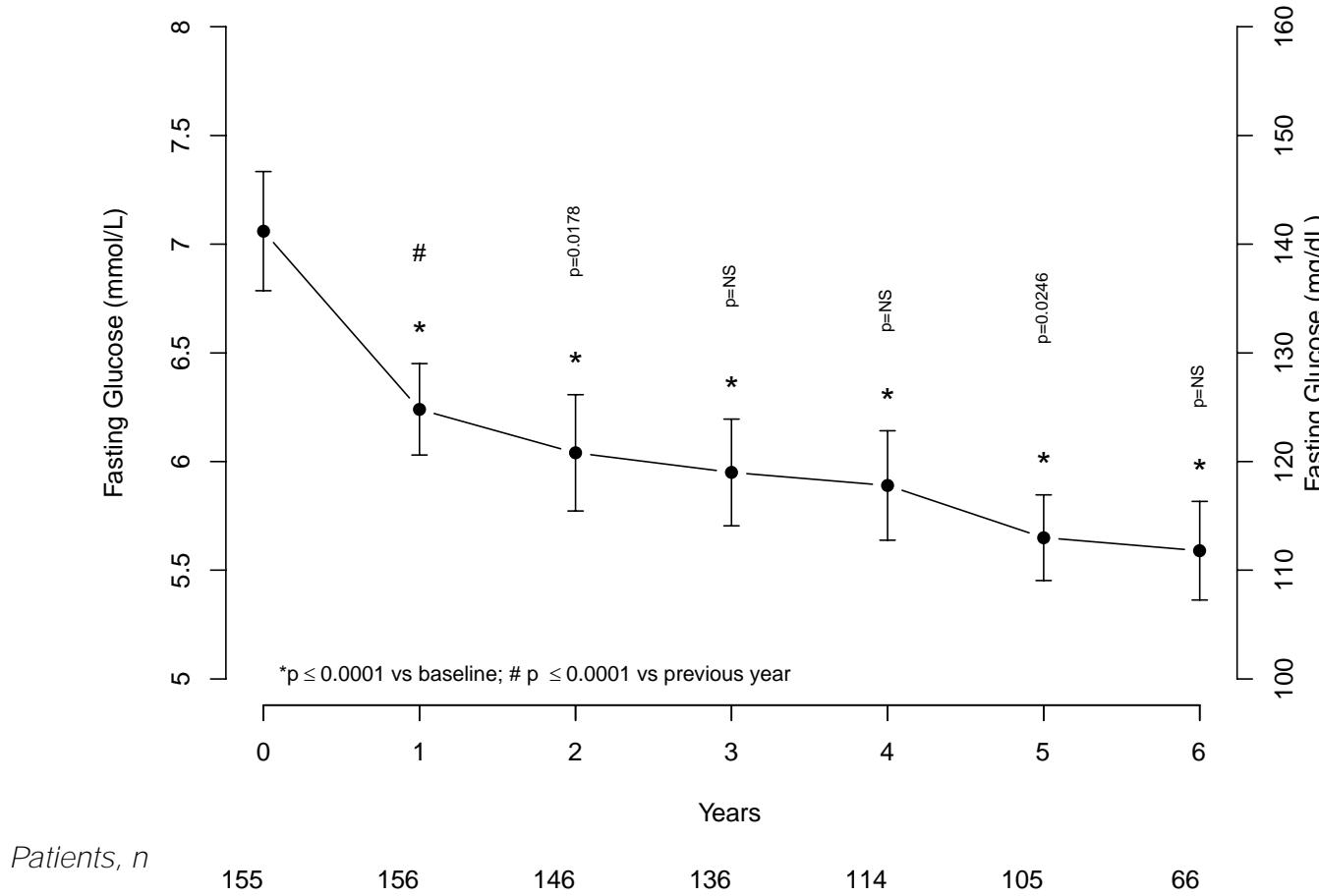
Baseline 7.9 %



HbA_{1c} (%) in 156 Obese Hypogonadal Men with Type 2 Diabetes mellitus Treated with Testosterone Undecanoate Injections for up to 6 Years

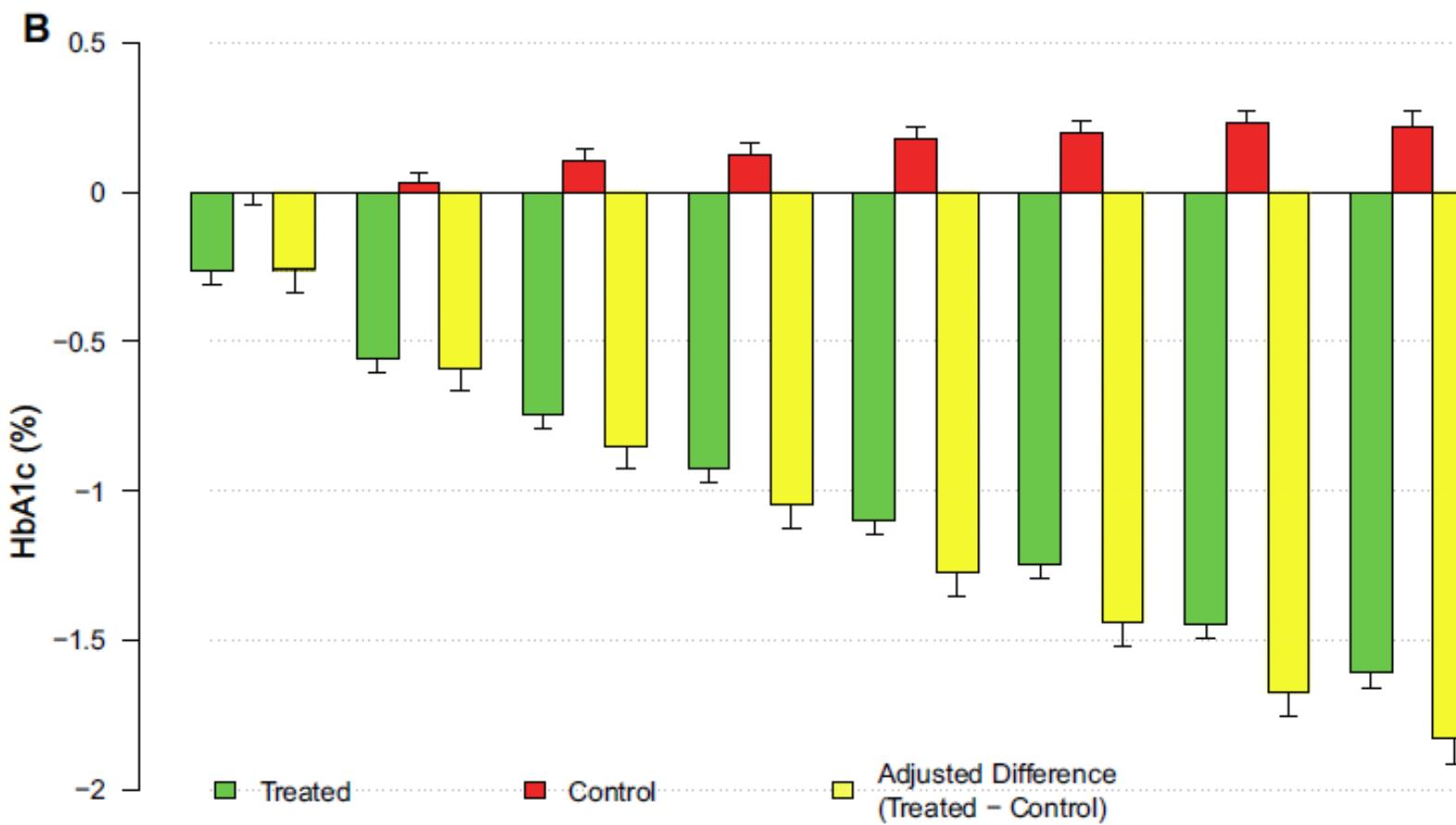


Fasting Glucose (mg/dL or mmol/L) in 156 Obese Hypogonadal Men with Type 2 Diabetes mellitus Treated with Testosterone Undecanoate Injections for up to 6 Years



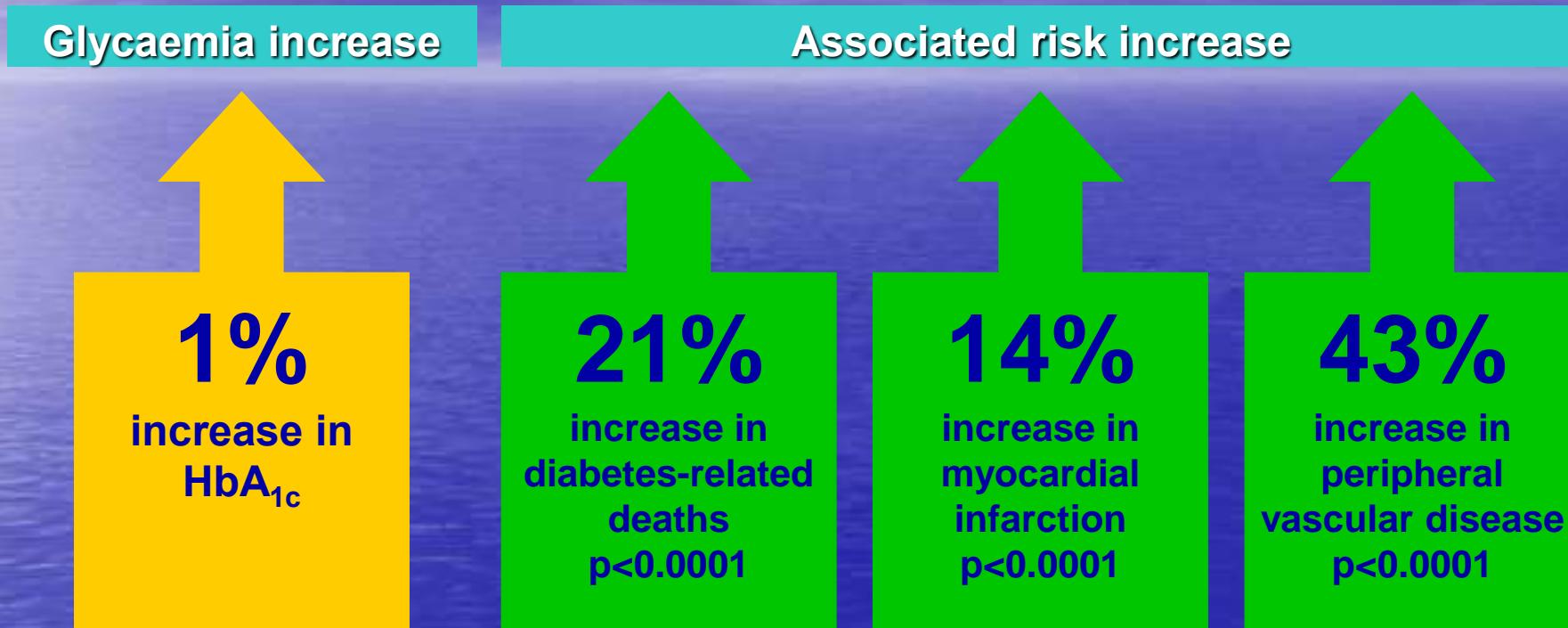
Changes in HbA_{1c} in Total Testosterone-Treated and Untreated Groups

Yellow bars show the estimated mean difference between groups, adjusted for baseline age, weight, waist circumference, fasting glucose, lipids, blood pressure, and quality of life (measured by AMS)



	1 Year	2 Years	3 Years	4 Years	5 Years	6 Years	7 Years	8 Years
Treated	241	241	225	197	147	119	97	85
Control	288	294	295	281	280	246	164	55

HbA_{1c} – relationship with CV risk

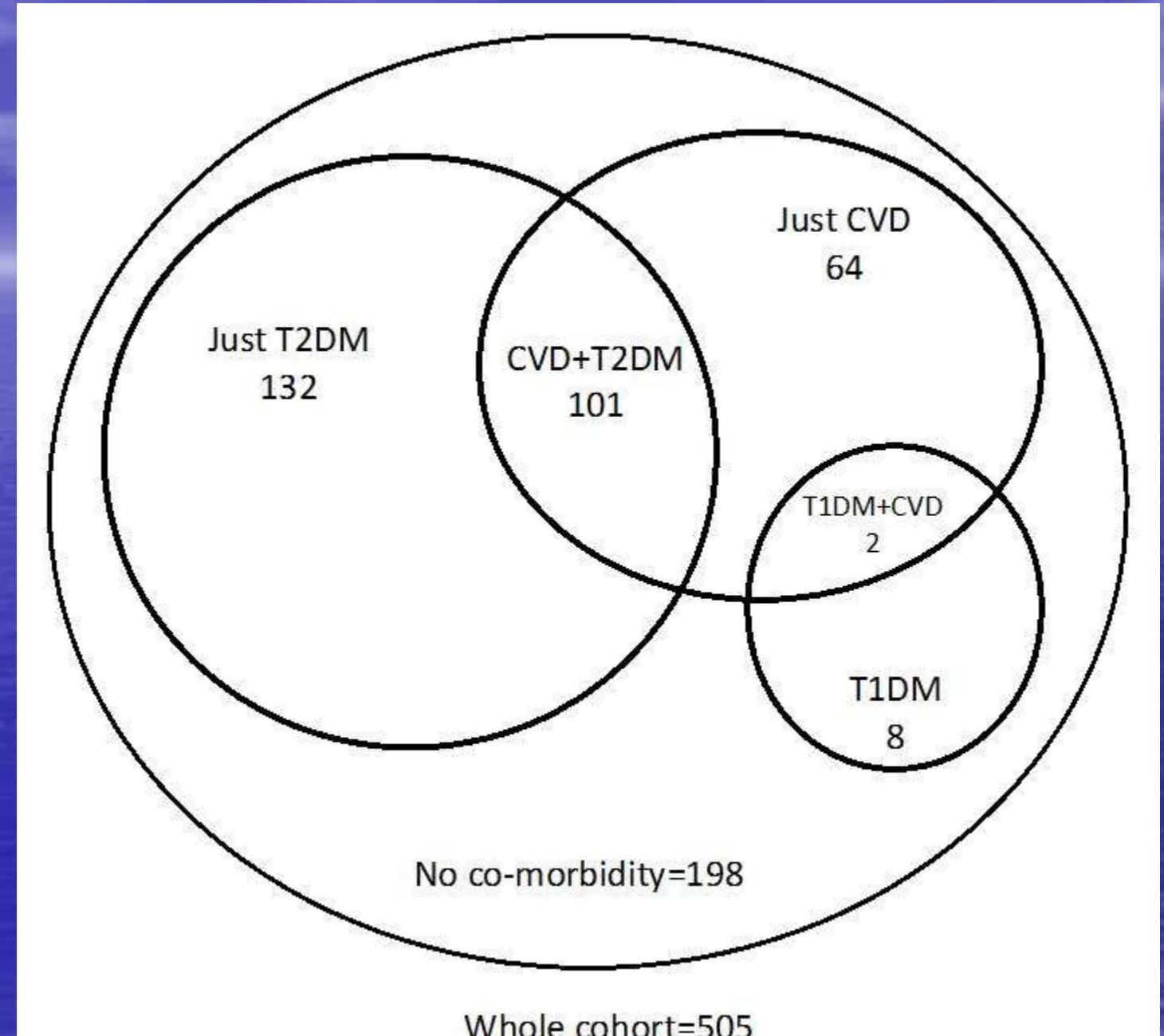


Audit Patients by Disease Category

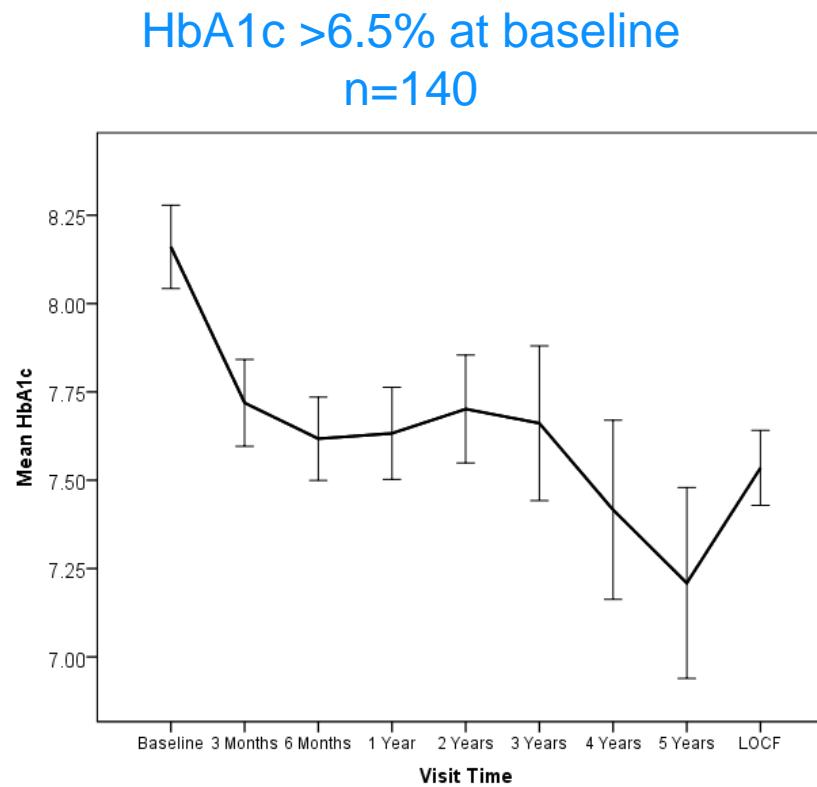
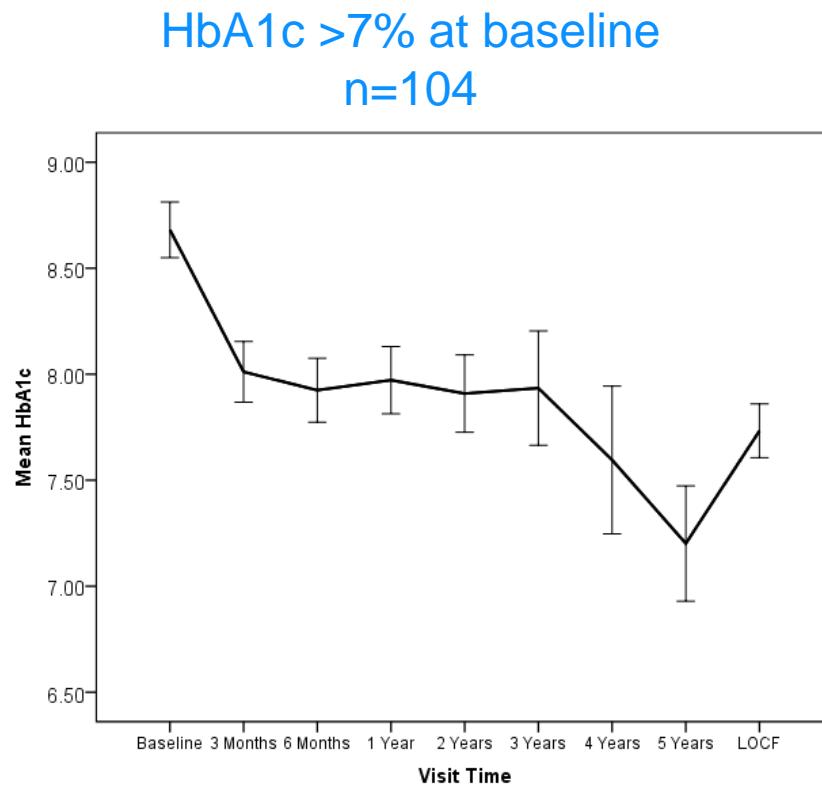
N=505

Mean F/U 4.94yrs

TRT 2387.6 patient yrs



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



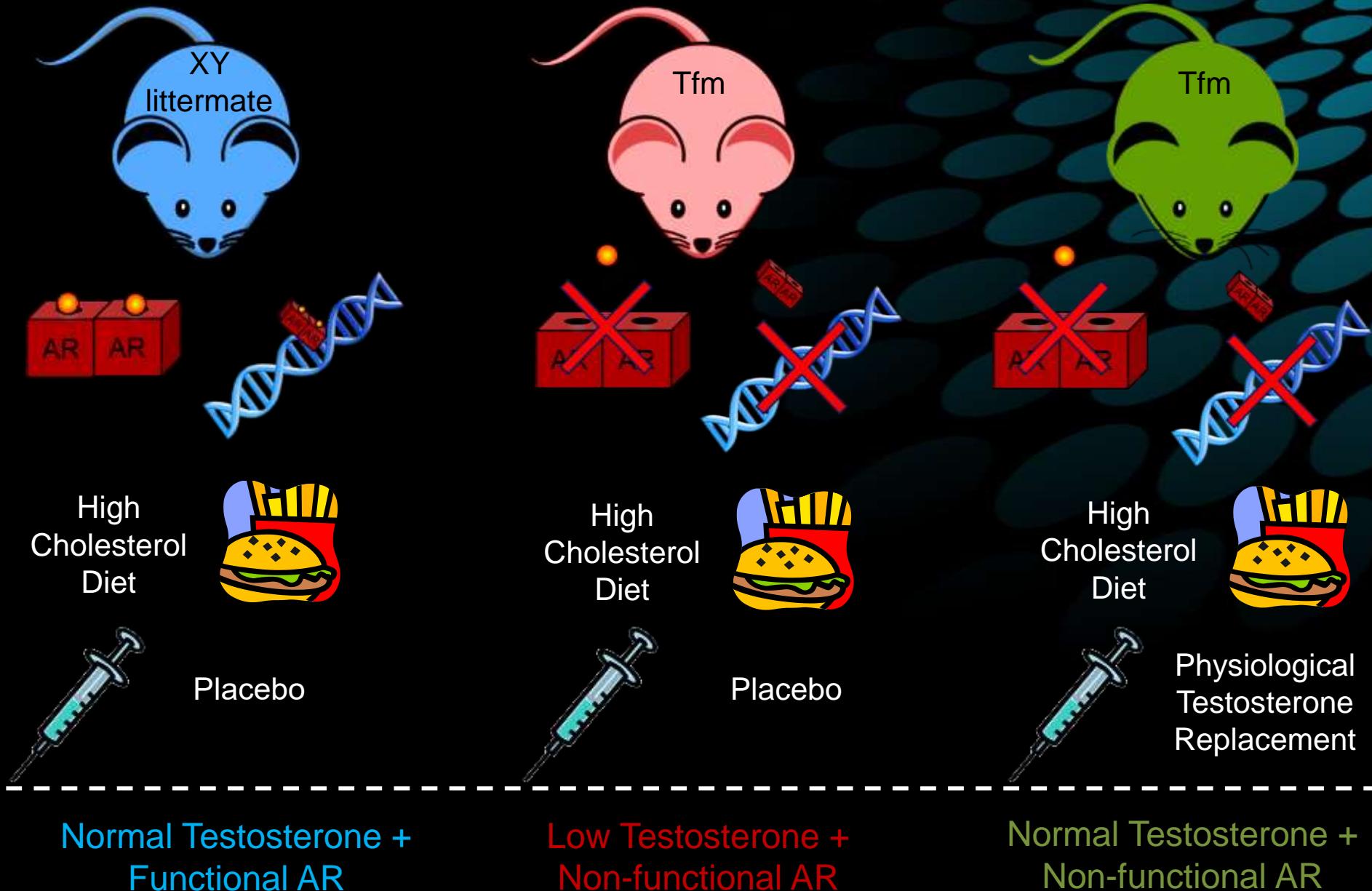
BASELINE COHORT DATA

	Total Cohort n=505		T2DM Patients n=232		CVD Patients n=167		No Comorbidities n=196	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Age (years)	<u>59.98</u>	14.42	<u>63.41</u>	12.85	<u>67.19</u>	11.36	<u>53.23</u>	15.03
Testosterone (nmol/L)	<u>7.09</u>	2.53	<u>7.35</u>	2.69	<u>7.14</u>	2.06	<u>6.81</u>	2.45
SHBG (nmol/L)	25.15	18.96	23.62	10.50	24.83	13.22	25.72	27.87
Estrogen (nmol/L)	124.73	45.50	119.84	43.85	116.82	46.10	130.39	48.41
LH (nmol/L)	5.53	5.89	5.42	4.14	6.08	5.89	5.10	6.48
FSH (nmol/L)	8.91	10.65	8.55	7.66	9.57	10.89	8.59	11.75
PSA (ng/ml)	1.06	1.02	1.07	1.04	1.16	1.04	0.96	0.91
Hb (g/dL)	14.30	1.25	14.07	1.30	14.05	1.16	14.64	1.18
HCT (%)	0.42	0.03	0.41	0.03	0.42	0.03	0.42	0.03
HbA1c (%)	7.24	1.64	7.57	1.44	7.25	1.49	5.90	1.95
Total Cholesterol (mmol/L)	4.48	1.14	<u>4.09</u>	0.90	<u>4.12</u>	.91	<u>5.19</u>	1.20
Triglycerides (mmol/L)	2.39	1.55	<u>2.45</u>	1.59	<u>2.17</u>	1.07	<u>2.48</u>	1.60
LDL (mmol/L)	2.36	0.96	<u>1.98</u>	0.70	<u>2.07</u>	0.77	<u>3.02</u>	1.04
HDL (mmol/L)	1.10	0.31	<u>1.05</u>	0.28	<u>1.10</u>	0.33	<u>1.17</u>	0.31
AST (U/L)	28.45	13.58	29.08	14.71	30.04	14.19	27.18	11.53
ALT (U/L)	35.16	20.78	36.41	23.70	33.80	19.75	33.71	16.25
Albumin (g/L)	44.28	3.27	44.14	3.11	44.24	3.68	44.88	2.74
Weight (kg)	103.7	23.2	<u>110.1</u>	24.1	<u>104.3</u>	21.2	<u>98.3</u>	20.1
Waist Circumference (cm)	115.7	17.0	<u>120.6</u>	17.1	<u>115.7</u>	12.8	<u>110.1</u>	16.1
Systolic BP (mmHg)	140	17	141	17	140	18	137	16
Diastolic BP (mmHg)	80	10	78	10	77	10	82	10
BMI (kg/m ²)	33.44	6.65	<u>35.93</u>	6.68	<u>34.16</u>	6.03	<u>31.46</u>	5.78

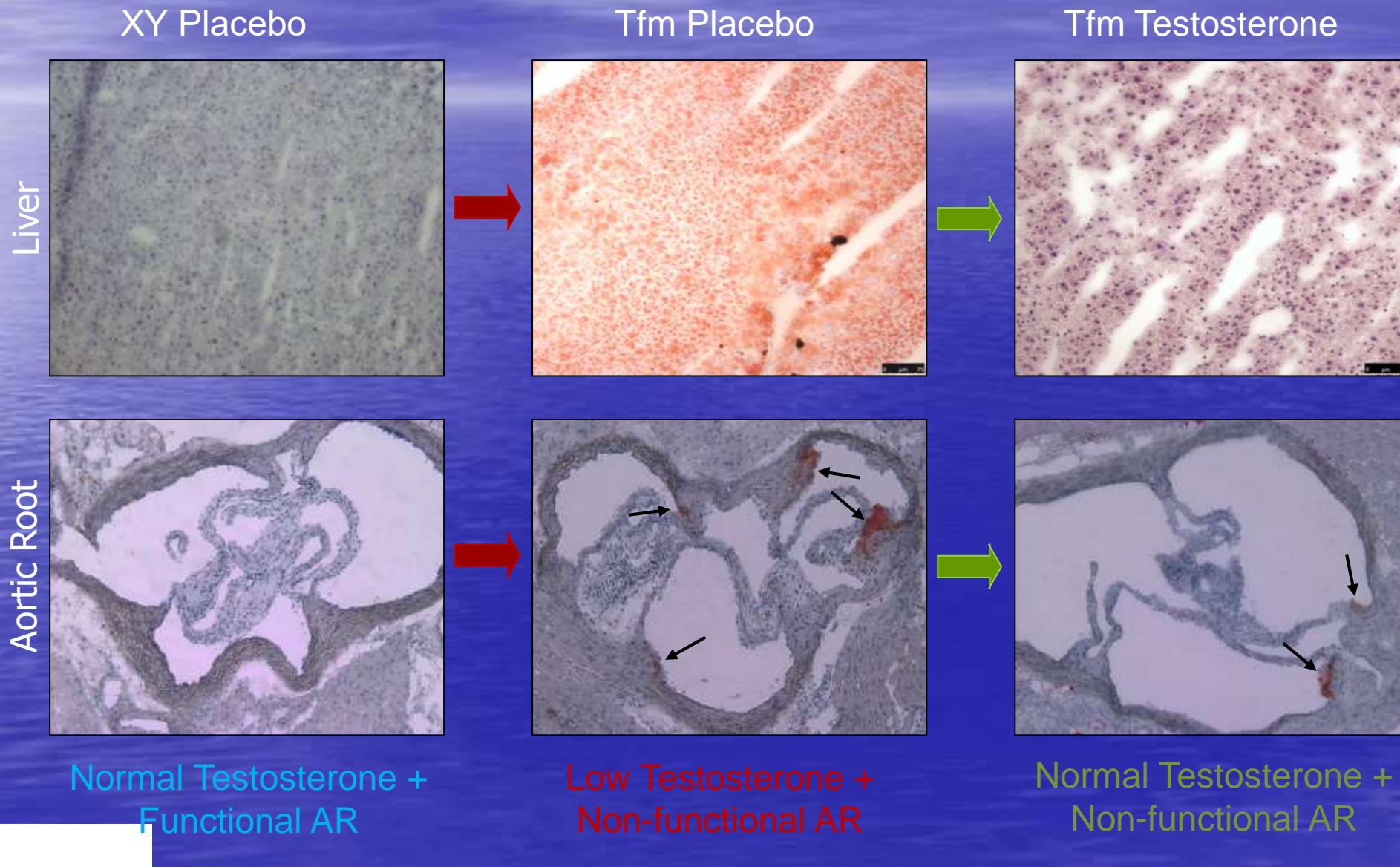
DIFFERENTIAL EFFECT OF TRT BETWEEN PATIENTS WITH TYPE 2 DIABETES, CARDIOVASCULAR DISEASE and NO-COMORBIDITIES

	T2DM n=232			CVD n=167			No co-morbidities n=196		
	Mean	Std. Error Mean	Sig	Mean	Std. Error Mean	Sig	Mean	Std. Error Mean	Sig
Testosterone (nmol/L)	9.41000	0.80239	0.000	11.45410	0.98159	0.000	10.3133	0.71600	0.000
SHBG (nmol/L)	5.91786	2.26811	0.015	5.57059	1.58615	0.003	3.30000	2.23212	0.154
Oestrogen (nmol/L)	26.91111	12.47563	0.037	52.00000	21.29930	0.023	32.9411	13.80629	0.030
PSA (ng/ml)	0.41679	0.10136	0.000	0.44165	0.11391	0.000	0.27838	0.07119	0.000
Haemoglobin (g/dl)	0.54231	0.10434	0.000	0.57980	0.13019	0.000	0.72689	0.10476	0.000
Haematocrit (%)	0.02374	0.00349	0.000	0.02571	0.00401	0.000	0.03115	0.00341	0.000
Total Cholesterol (mmol/L)	-0.31042	0.07823	0.000	-0.33690	0.09361	0.001	-0.56383	0.15350	0.001
Triglycerides (mmol/L)	-0.09588	0.10721	0.373	-0.23671	0.11924	0.051	-0.47930	0.20114	0.021
LDL (mmol/L)	-0.22557	0.07533	0.003	-0.16828	0.09101	0.069	-0.44667	0.14214	0.003
HDL(mmol/L)	-0.04458	0.01479	0.003	-0.04375	0.02565	0.092	-0.06259	0.03503	0.079
AST (U/L)	-4.11628	1.47458	0.006	-1.88372	1.67623	0.267	1.06897	1.45027	0.467
ALT (U/L)	-5.79545	2.09718	0.007	-2.63043	1.78110	0.147	2.06452	2.79013	0.465
Albumin (g/L)	-0.19048	0.33852	0.575	-0.55814	0.67899	0.416	-0.19355	0.67269	0.776
Weight (Kg)	-2.42680	0.5844	0.000	-1.0551	0.5660	0.065	0.4168	0.5256	0.429
Waist (cm)	-1.54620	0.6753	0.024	-0.0255	0.8276	0.976	-1.3061	0.8388	0.126
BMI (kg/m ²)	-0.87603	0.22462	0.000	-0.11379	0.19416	0.560	0.22361	.18272	0.223
Systolic BP (mmHg)	-2.53400	1.372	0.066	-1.000	1.873	0.595	1.301	1.361	0.341
Diastolic BP (mmHg)	-0.75000	0.820	0.362	-0.792	0.966	0.414	0.483	0.924	0.602
HbA1c (%)	-0.23291	0.09797	0.019						

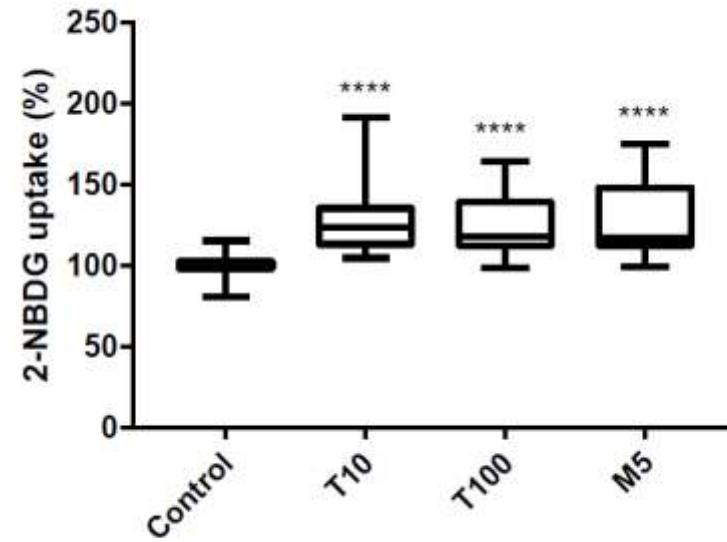
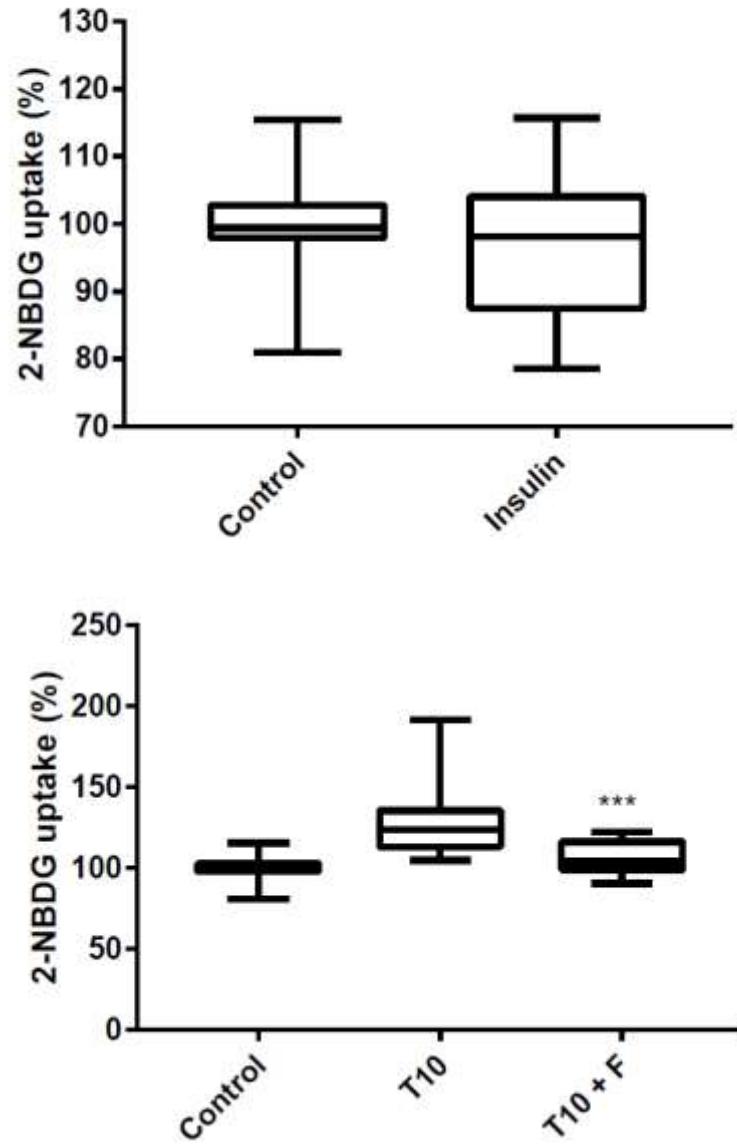
Testicular Feminized (Tfm) Mouse



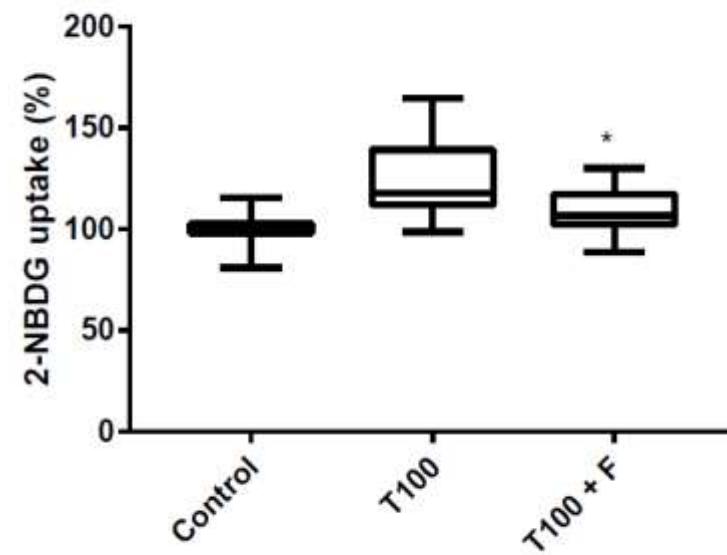
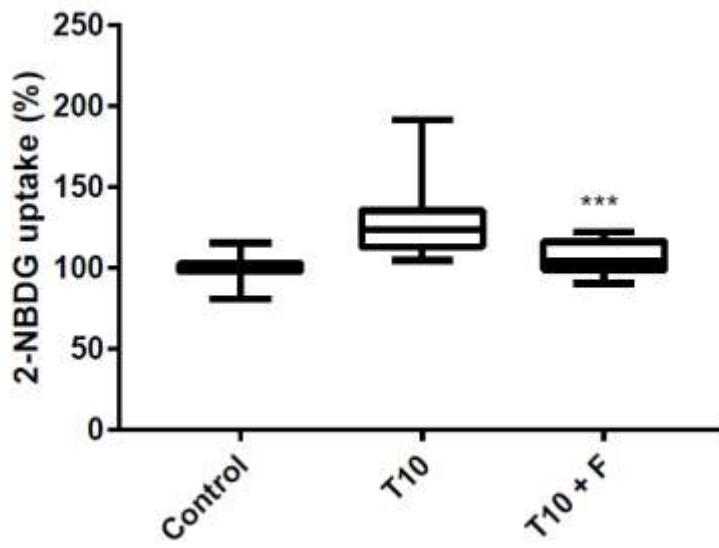
Lipid Deposition



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



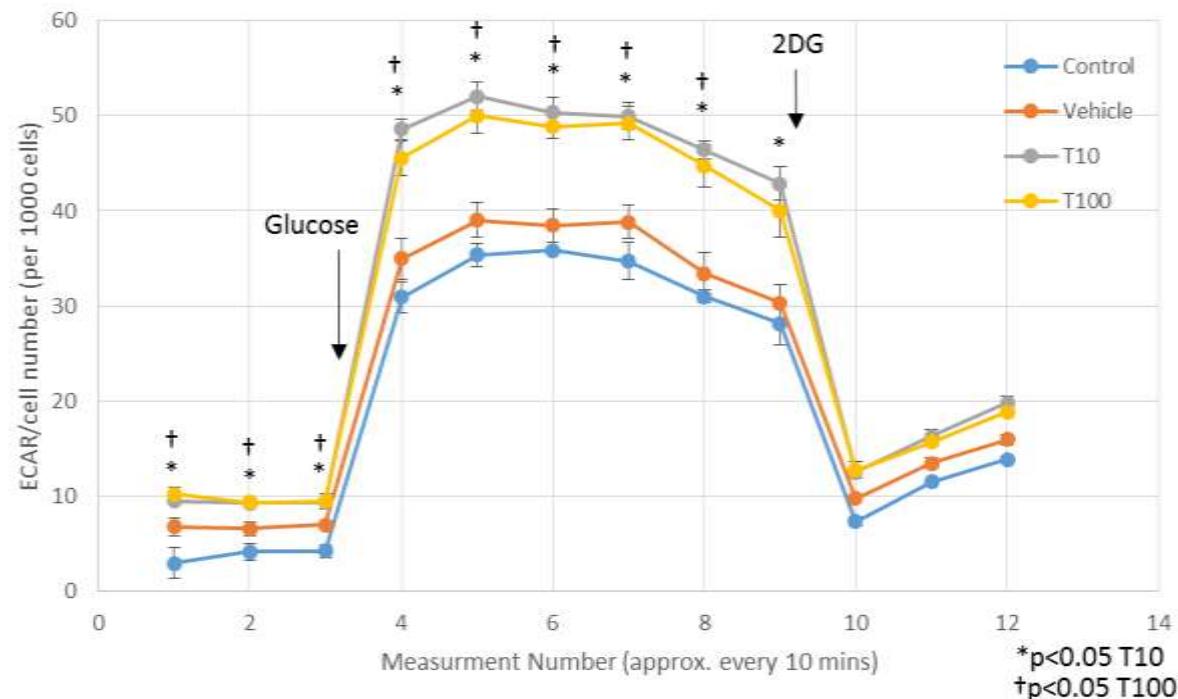
M=Metformin
F=Flutamide



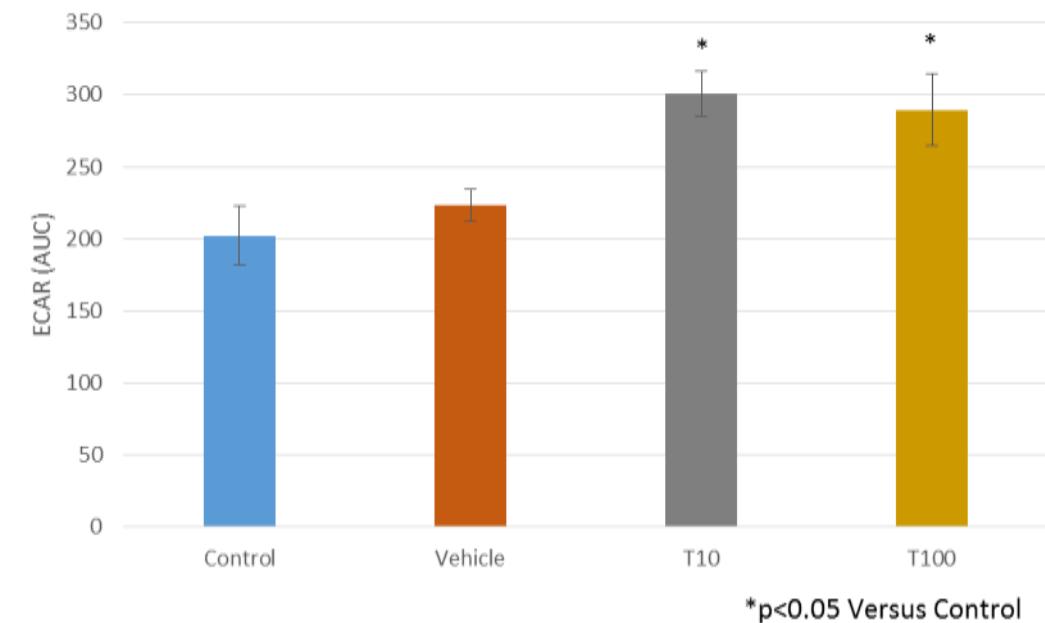
Unpublished

Effect of Testosterone on Rate of Glycolysis in HepG2 Liver Cells

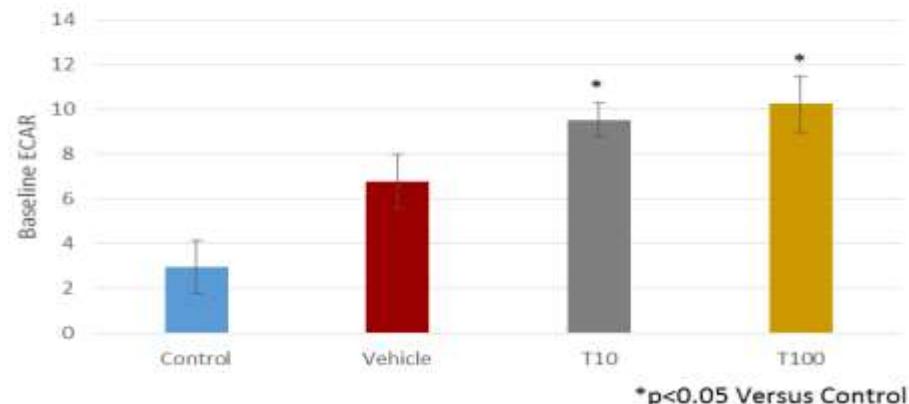
Extracellular Acidification Rate (ECAR)



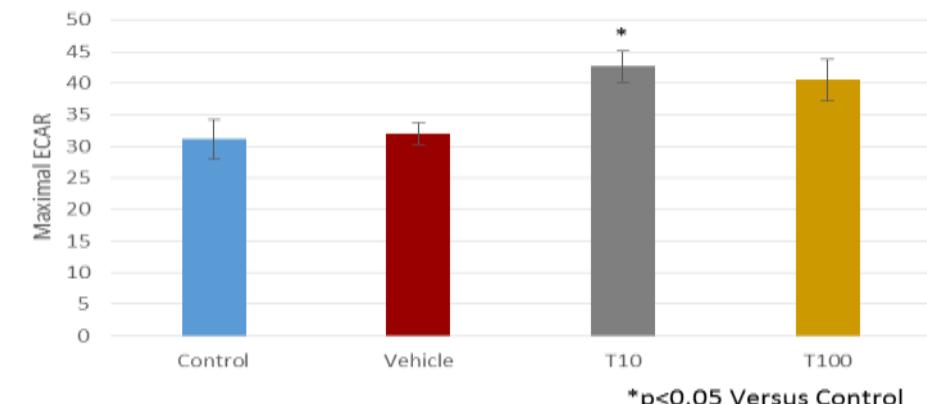
ECAR (AUC)



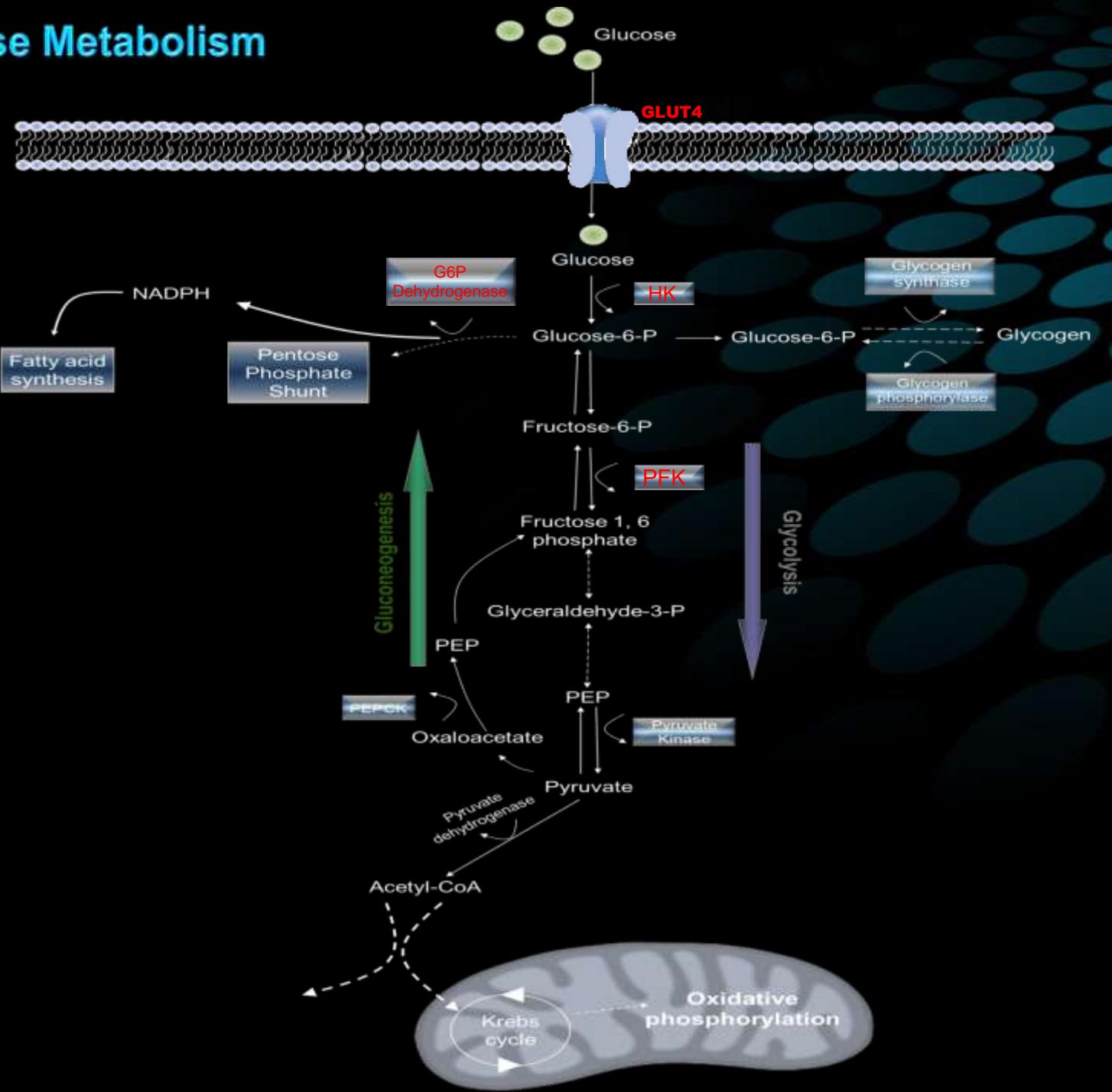
Baseline ECAR



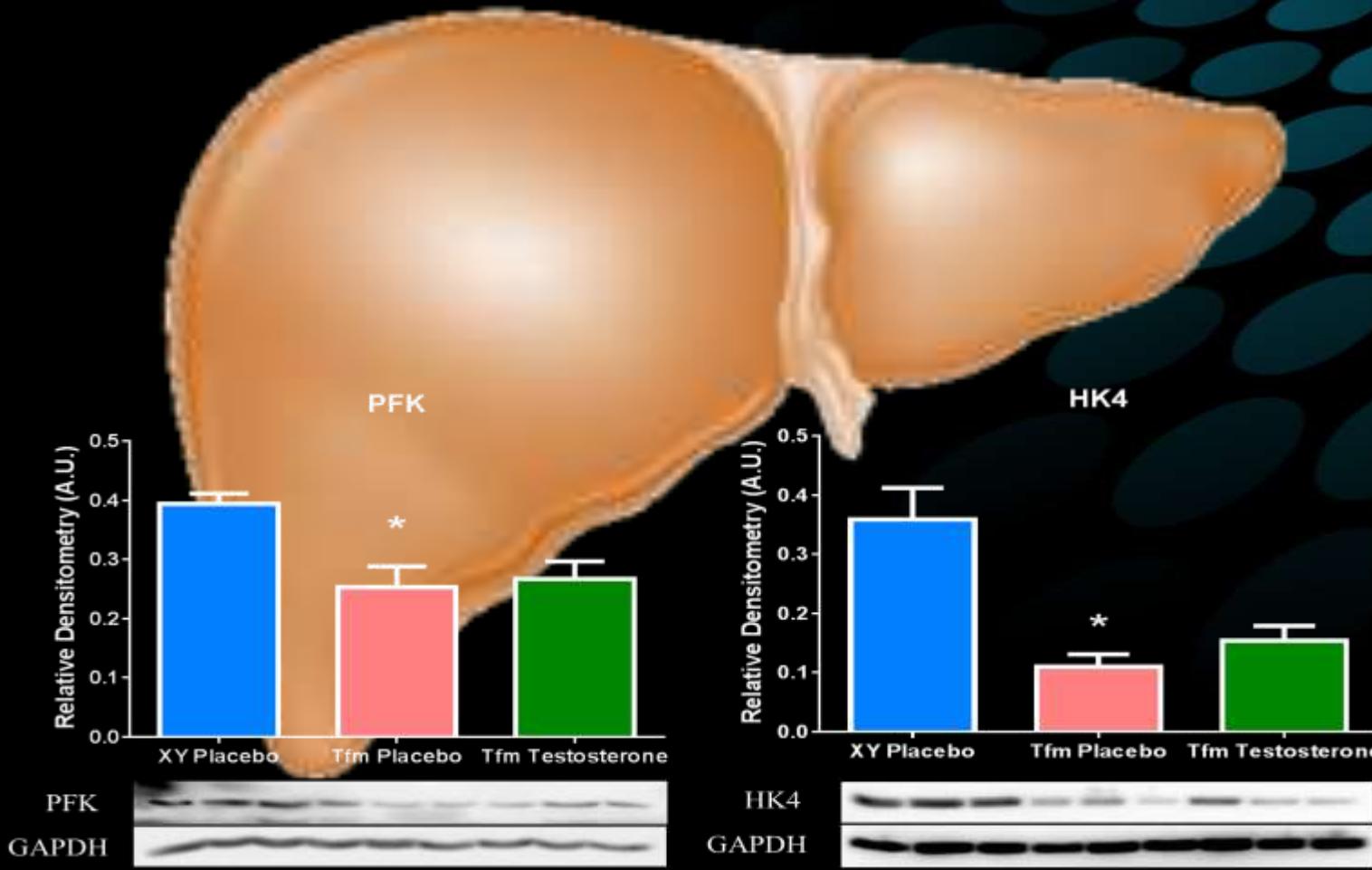
Maximal ECAR



Glucose Metabolism

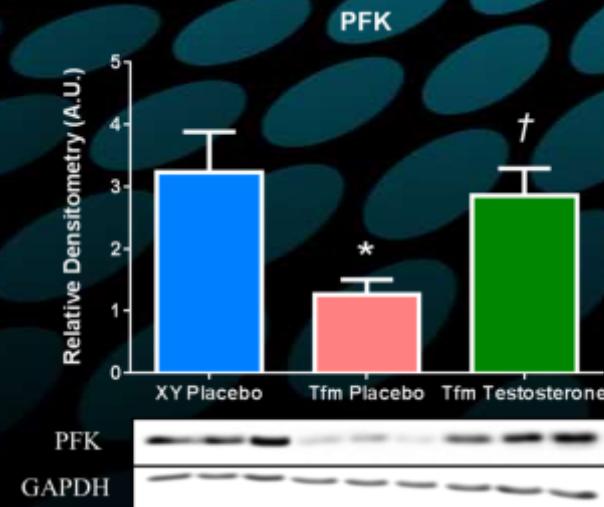
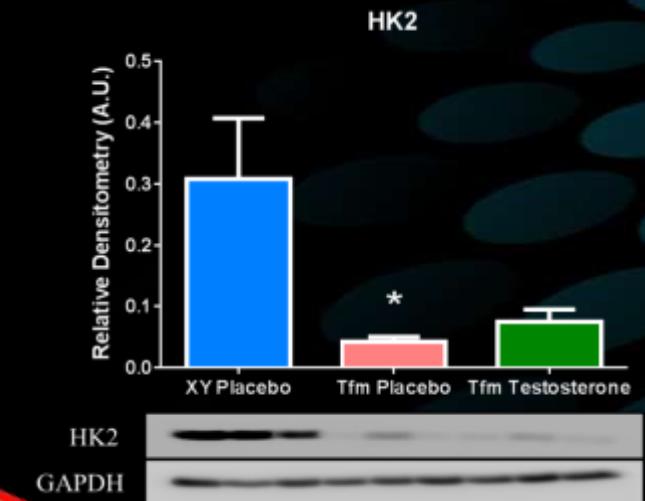
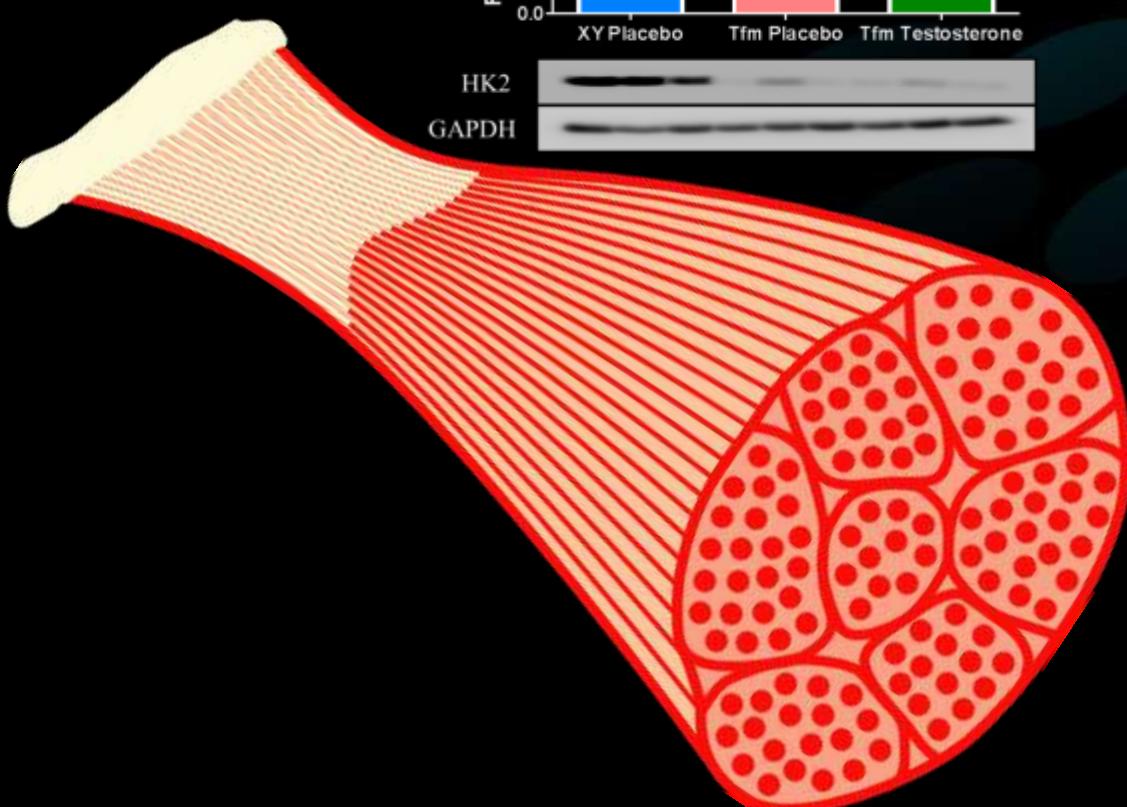
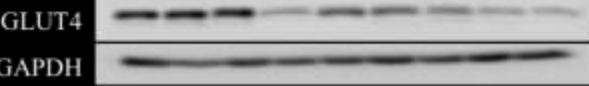
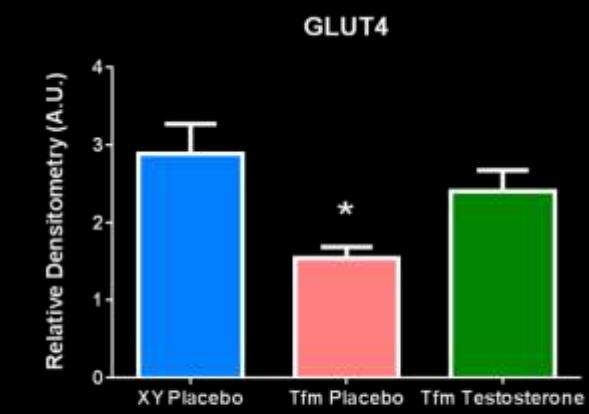


Effect of Testosterone Status on Regulatory Enzymes Of Glycolysis in the Tfm mouse



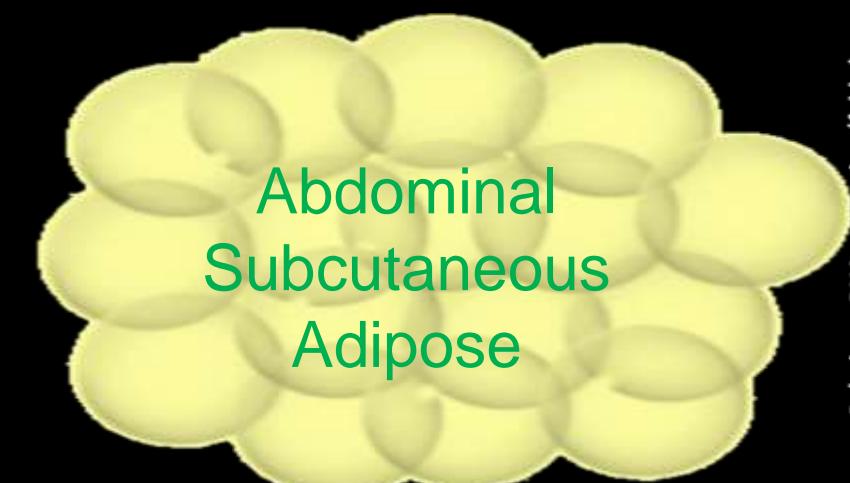
Kelly DM & Jones TH
Endocrine 2016;54:504-515

Testosterone and the Expression of the GLUT4 Transporter and Regulatory Enzymes of Glycolysis

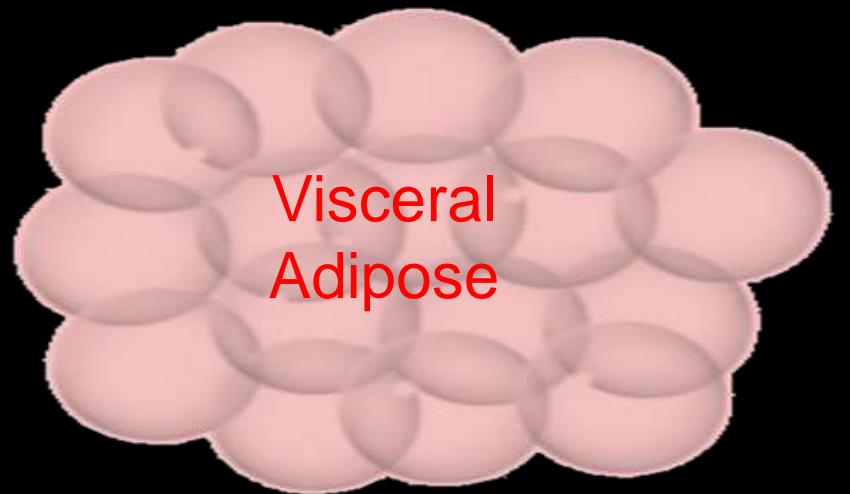


Kelly DM & Jones TH
Endocrine 2016;54:504-515

Glucose Metabolism

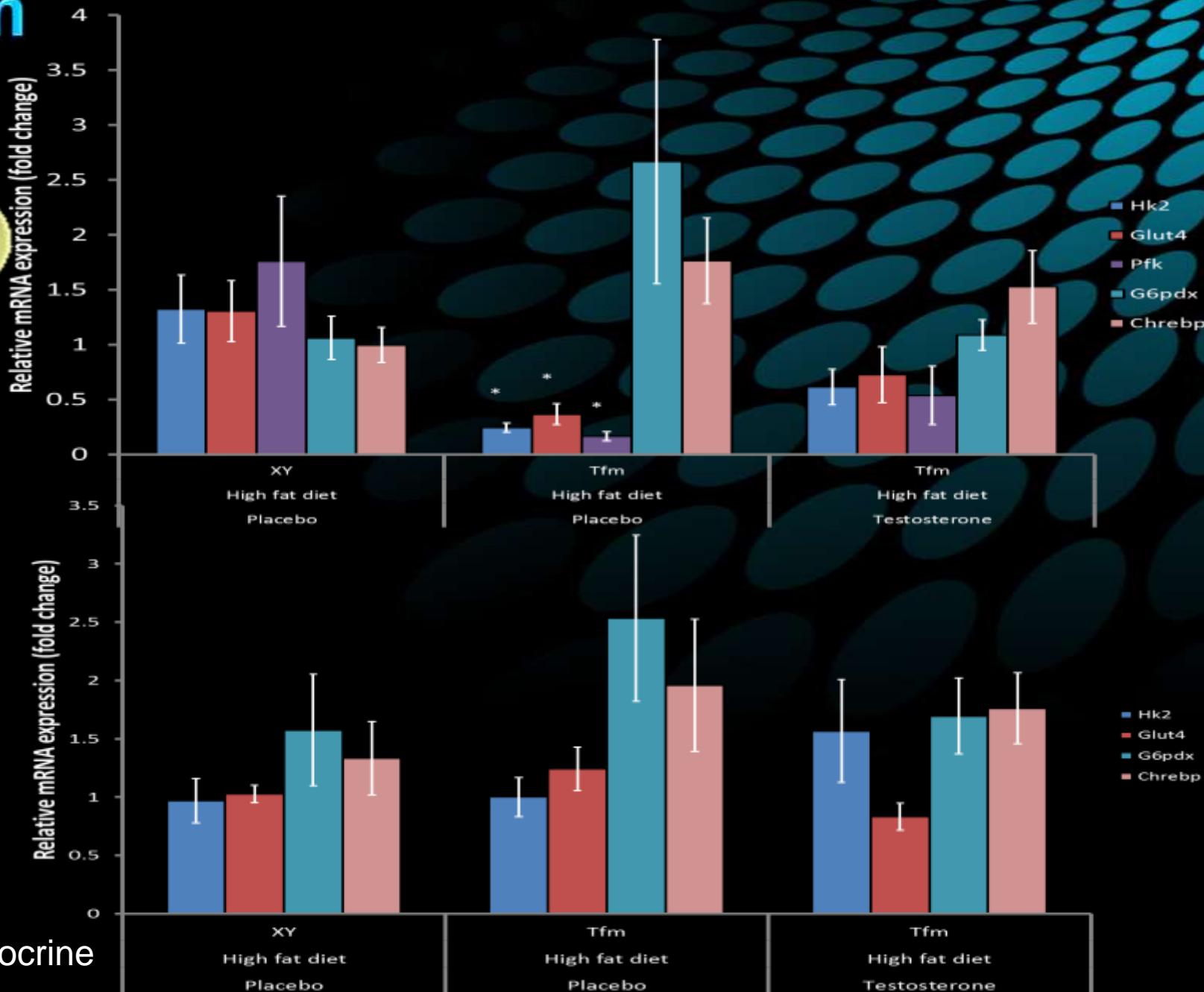


Abdominal
Subcutaneous
Adipose

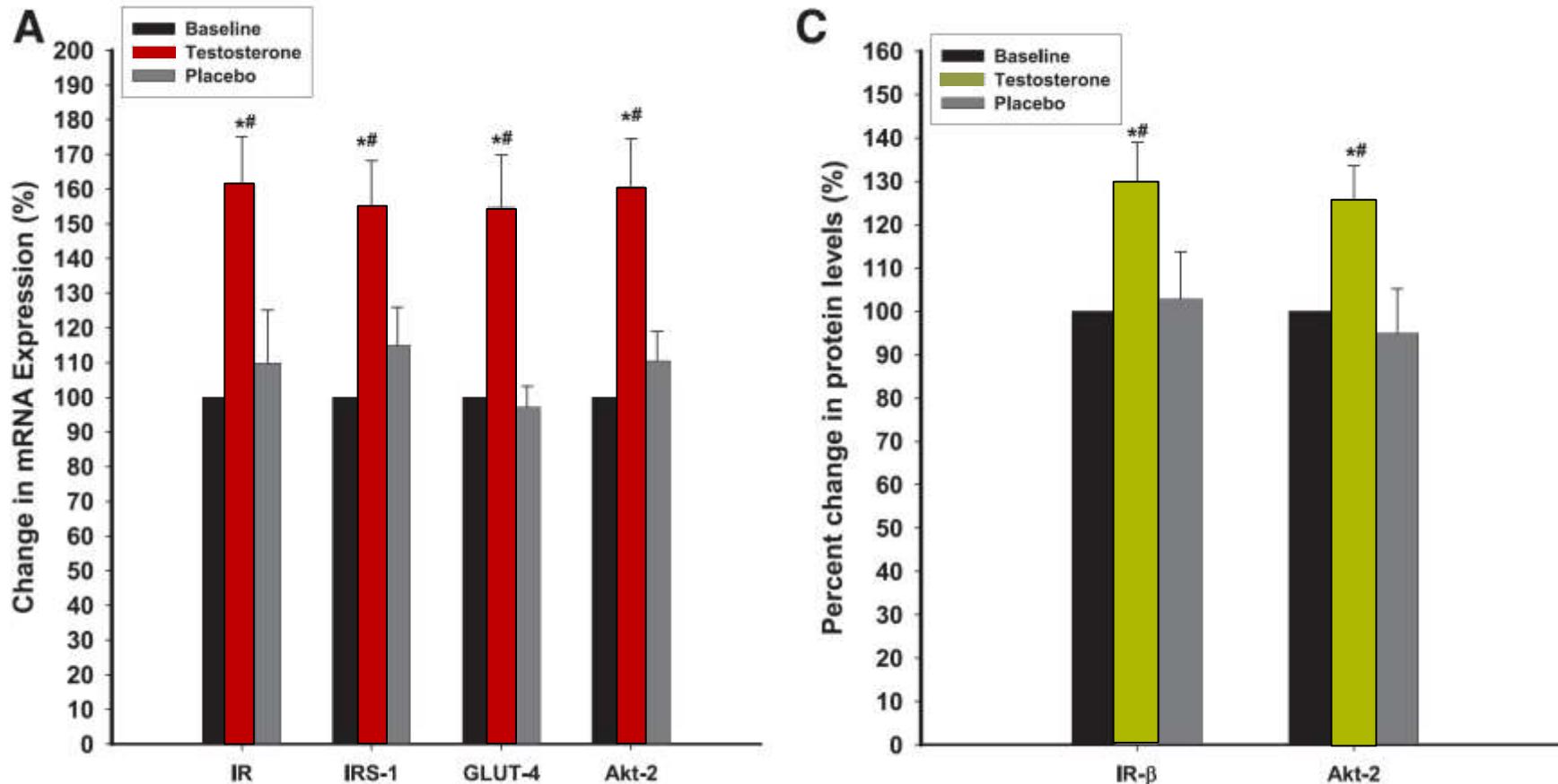


Visceral
Adipose

Kelly DM & Jones TH Endocrine
2016;54:504-515



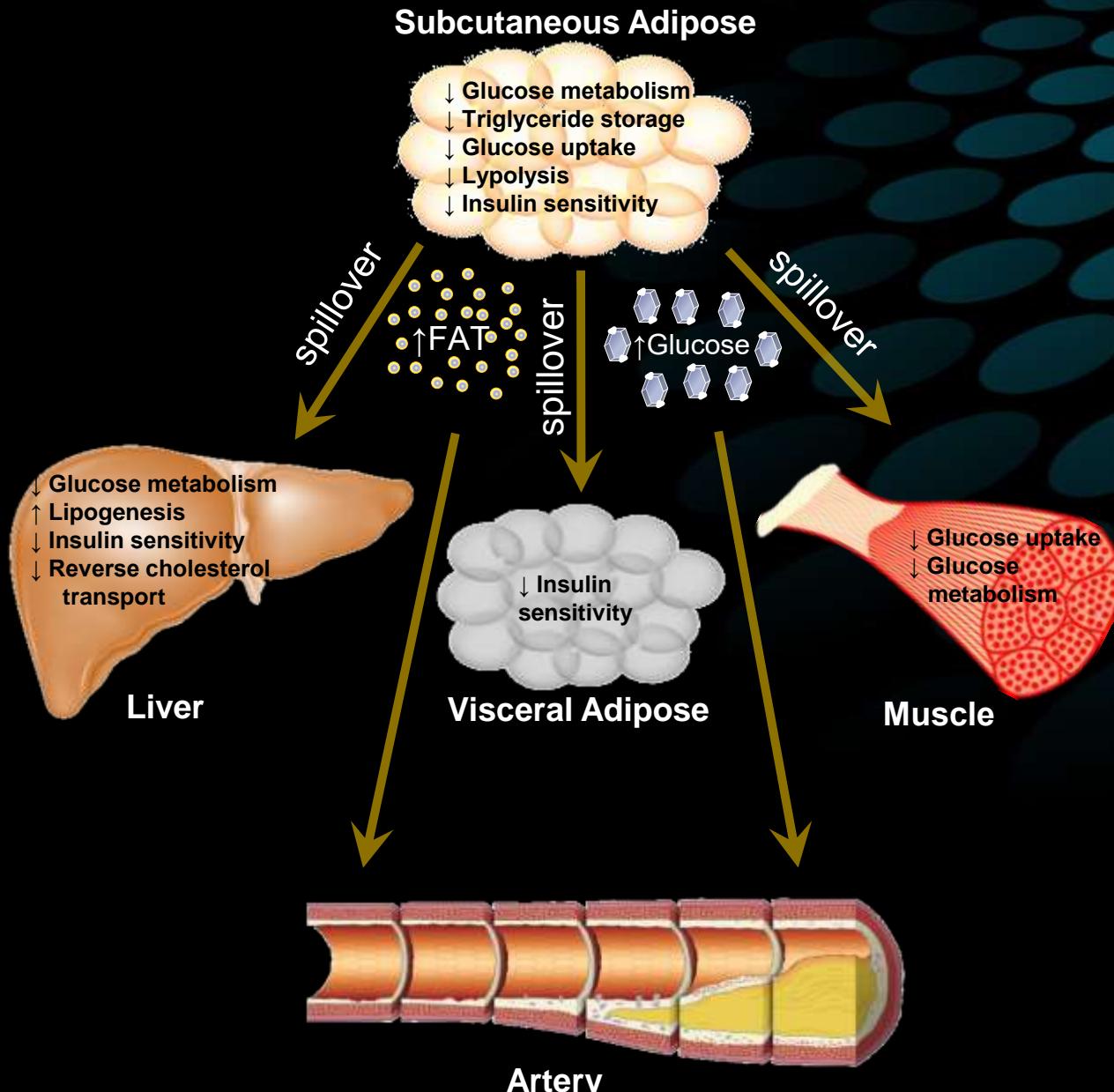
Functional background: Genetic changes induced by TRT



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

TESTOSTERONE BUFFER and SPILLOVER HYPOTHESIS

TESTOSTERONE DEFICIENCY



Science Summary

- Testosterone may have tissue-specific metabolic effects to improve glucose utilisation and insulin sensitivity in liver, subcutaneous adipose and muscle tissue.
- Testosterone may improve lipid metabolism in liver and subcutaneous adipose tissue.
- Some of these effects are, at least in part, androgen receptor independent.
- Testosterone may increase the buffering capacity of subcutaneous adipose to protect against energy imbalance and fat overspill into liver and arterial vessels.
- This study adds mechanistic insight to the observed cardiometabolic clinical benefit of testosterone in men with T2D and metabolic syndrome.

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NEWS

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Health

Testosterone 'could prevent heart and diabetes deaths'

By James Gallagher
Health editor, BBC News website, San Diego

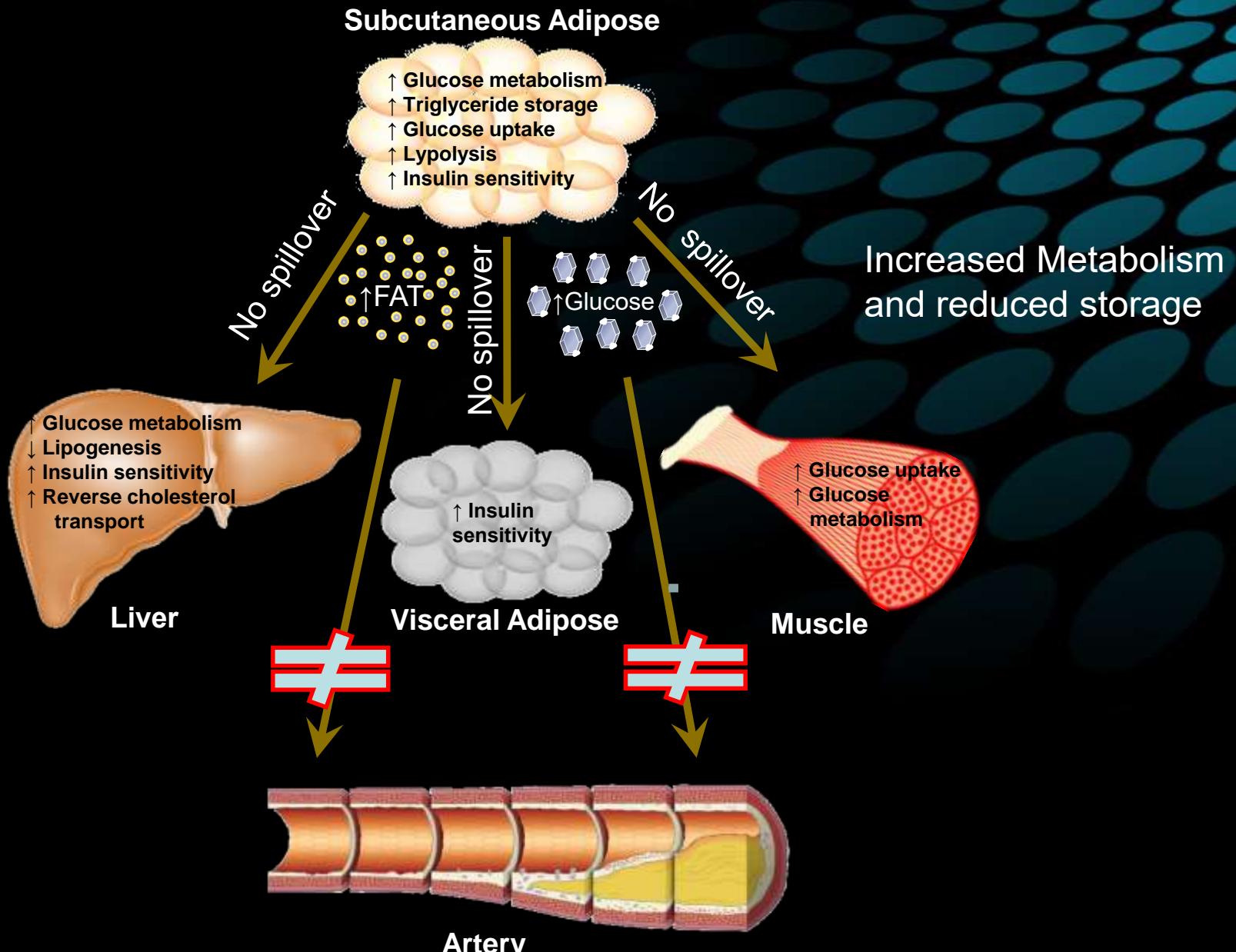
© 14 March 2015 | Health



Boosting men's testosterone levels could potentially reduce deaths from heart disease and type 2 diabetes, UK doctors and scientists say. A team in Sheffield has shown the sex hormone has a "major impact" on the way sugar and fat are handled by the body.

TESTOSTERONE BUFFER and SPILLOVER HYPOTHESIS

TESTOSTERONE
REPLETE STATE



Summary

- Type 2 Diabetes is a terrible and serious disease associated with reduced QOL, major complications and premature death.
- High prevalence of Male Hypogonadism
- Low Testosterone is associated with an ↑ CV Risk Profile
- And all-cause and CV mortality and CV events
- TRT to the normal range reduces body fat, waist circumference, BMI and increases lean mass
- TRT ↑ Insulin Sensitivity, ↓ HbA1c, ↓ Total and LDL cholesterol, ↓ TNFa & may improve fatty liver
- TRT improves mortality and may reduce CV events