Measuring Testosterone towards reasonable application in the male metabolic syndrome

Or

How older age, fatness and sophistication complicate the practice of medicine

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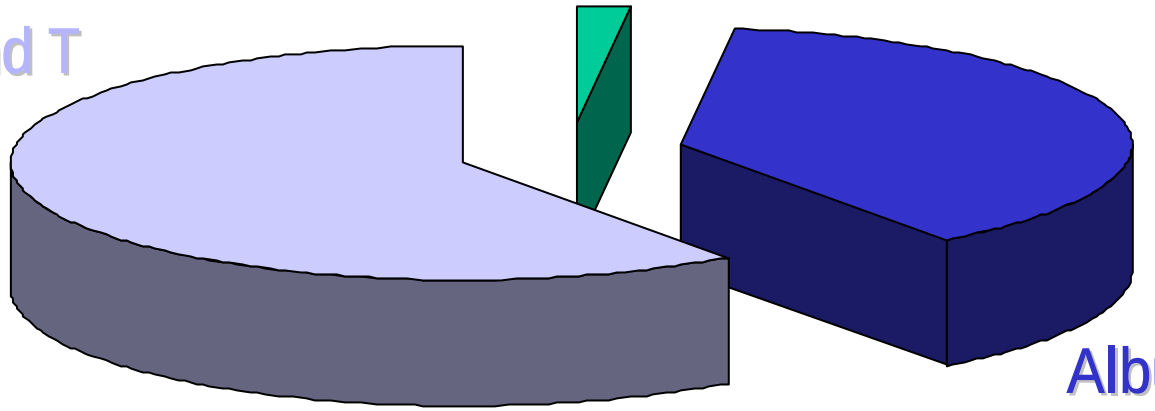
Bio-available testosterone (BioT)

Circulating serum testosterone:



BioT = Free T + Albumin bound T

How well can we estimate bio-available testosterone?

Advantages of BioT over TotalT

BioT has been shown to correlate well with clinical parameters such as:

- bone mineral density
- sexual function
- muscle mass
- development of generalised fragility

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Measuring BioT

Using a radioactive tracer and ammonium sulphate to precipitate SHBG and its bound steroids.

Testosterone is then either measured in the supernatant or in the precipitate after reconstitution.

Non-automated

Time consuming

Calculating BioT

- Vermeulen et al. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endo & Metab 1999;84(10):3666-72.
- Sodergard et al. Calculation of free and bound fractions of testosterone and estradiol-17 beta to human plasma proteins at body temperature. J Steroid Biochem 1982;16:801-10.
- Emadi-Konjin et al. Evaluation of an algorithm for calculation of serum “bioavailable” testosterone. Clin Biochem 2003;36:591-6.
- Morris et al. A mathematical comparison of techniques to predict biologically available testosterone in a cohort of 1072 men. Eur J Endocrinol 2004;151:241-9.

Convenient & cheap

Free & Bioavailable Testosterone calculator

These calculated parameters more accurately reflect the level of bioactive testosterone than does the sole measurement of total serum testosterone. Testosterone and dihydrotestosterone (DHT) circulate in plasma unbound (free approximately 2 - 3%) ,bound to specific plasma proteins (sex hormone-binding globulin SHBG) and weakly bound to nonspecific proteins such as albumin. The SHBG-bound fraction is biologically inactive because of the high binding affinity of SHBG for testosterone. Free testosterone measures the free fraction, bioavailable testosterone includes free plus weakly bound to albumin.

Albumin	43	g/L
SHBG		nmol/L
Testosterone		nmol/L

Calculate

Explanation and examples

Free Testosterone	
Bioavailable Testosterone	

Disclaimer: Results from this calculator should NOT be solely relied upon in making (or refraining from making) any decision in any case/ circumstances without the prior consultation of experts or professional persons. No responsability whatsoever is assumed for its correctness or suitability for any given purpose.

WARNING! The calculated free and bioavailable testosterone are reliable in most clinical situations, but should not be relied upon in situations with potential massive interference by steroids binding to SHBG; e.g. in women during pregnancy, in men during treatment inducing high levels of DHT (e.g. transdermal DHT, oral testosterone) or mesterolon

This calculator was developed at the Hormonology department, University Hospital of Ghent, Belgium. If you have suggestions to improve this calculator, or for further questions or help contact us Dr. Tom Fiers or Prof. Dr. J.M. Kaufman

Try It!

- Where do I find the normal range for BT?
- Do all testosterone assays fit?
- Do all SHBG assays fit?

Try it some more!

- Total testo -300ng/dl
- SHBG- 71 nmol/l (highest for men)
- BT-81.2ng/dl
- In other words, if your total testosterone is 300ng/dl you may not have low BT even if the SHBG is high…….

Try it again, sir

- Obese 67y/o man
- Lower SHBG in obese subjects. Mean for obese subjects with met syndrome in one assay 24nmol/l
- Testo 200ng/dl (US Endo Soc cutoff for hypogondism)
- Calculated BT-106ng/dl –still normal!!!!!

Examples of use

Calculated bio-available testosterone levels and depression in middle-aged men. Psychoneuroendocrinology 2006;31:1029-35

Serum sex hormone and plasma homocysteine levels in middle-aged and elderly men. Eur J Endocrinol 2006;155:887-93

A population-level decline in serum testosterone levels in American men. J Clin Endocrinol Metab 2006; Oct 24.

Hypogonadism in male patients with cancer. Cancer 2006;106:2583-91

Association of bio-available, free and total testosterone with insulin resistance: influence of sex hormone binding globulin and body fat. Diab Care 2004;27(4):861-8

The association of sex hormone levels with poor mobility, low muscle strength and incidence of falls among older men and women. Clin Endocrinol Oxf 2005;63:152-60

Disclaimer:

We are not responsible, ask the professionals

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Project background

"Algorithms to calculate BioT must be revalidated in the local setting, otherwise over- or underestimation of BioT concentrations can occur."

(i) Validate an LC-MS/MS method to measure BioT

(ii) Compare the results to calculated estimates from our routine testosterone and SHBG assays

LC-MS/MS method for BioT

1) Precipitation of SHBG with its bound steroids using cold saturated ammonium sulphate
2) Add d2-testosterone internal standard to the supernatant and perform a liquid-liquid extraction
3) Measure the remaining testosterone concentration by LC-MS/MS

Validation of LC-MS/MS method for BioT

- No ion suppression at the point where testosterone and d2-testosterone co-elute.
- Linear over the concentration range 0.26 – 162.5 nmol/L testosterone.
- Acceptable precision; the lowest QC gave a CV of less than 15% both within and between batches and the 3 higher QCs gave CVs of less than 10% both within and between batches.

Comparison

- 97 male serum samples
- LC-MS/MS measured BioT
- Roche E170 total testosterone
- Immulite SHBG
- 4 different published algorithms:

1) Vermeulen et al *[J Clin Endo & Metab 1999;84:3666-72]*
2) Sodergard et al *[J Steroid Biochem 1982;16:801-10]*
3) Emadi-Konjin et al *[Clin Biochem 2003;36:591-6]*
4) Morris et al *[Eur J Endocrinol 2004;151:241-9]*

Calculations 1

Vermeulen, Sodergard, Emadi-Konjin

$$BioT = [FT] + \{(k_{at} \times [alb] \times [FT]) / (1 + (k_{at} \times [FT]))\}$$

$$FT = \{-b + \sqrt{(b^2 + 4a[T])}\} / 2a$$

$$a = k_{at} + k_t + \{k_{at} \times k_t \times ([SHBG] + [alb] - [T])\}$$

$$b = 1 + (k_t \times [SHBG]) + (k_{at} \times [alb]) - ((k_{at} + k_t) \times [T])$$

k_{at} is the affinity constant for testosterone binding to albumin

k_t is the affinity constant for testosterone binding to SHBG

Calculations 2

Morris

$$BioT = e^{(-0.266 + (0.955 \times \ln[T]) - (0.288 \times \ln[SHBG])}$$

Measured BioT by ammonium sulphate precipitation then created a regression equation based on their measurements.

Results of comparison

	Mean BioT (nmol/L)	Mean BioT (% of total)	Range BioT (nmol/L)	Range BioT (% of total)
LC-MS/MS	5.5	39.0	0.26 – 17.2	6.7 – 86.5
Vermeulen et al	8.0	53.3	0.44 – 24.3	21.5 – 78.6
Sodergard et al	9.8	65.5	0.64 – 28.2	33.4 – 85.8
Emadi-Konjin et al	4.6	30.0	0.16 – 17.1	7.3 – 61.0
Morris et al	4.8	32.5	0.43 – 12.0	23.3 – 43.4

Why the differences?

- Different association constants
- Commutability of total testosterone and SHBG assays
- Fixed albumin concentration of 43 g/L

⟹ Unlikely that any one of these reasons alone could fully account for the large differences in BioT concentration seen.

Conclusions

None of the 4 algorithms tested with our routine testosterone and SHBG assays produced comparable BioT concentrations to our measured LC-MS/MS BioT concentration.

This further re-iterates the need for local revalidation of equations to predict BioT.

Conclusions

Although all methods of calculating or measuring BioT may be useful to show changes or patterns within a patient, an isolated value may have little meaning and can not be compared to other BioT values unless they were generated by the same method.

Calculation of Bioavailable and Free Testosterone in Men: A Comparison of 5 Published Algorithms

de Ronde et al, Clin Chem 52: 1777-1784, 2006

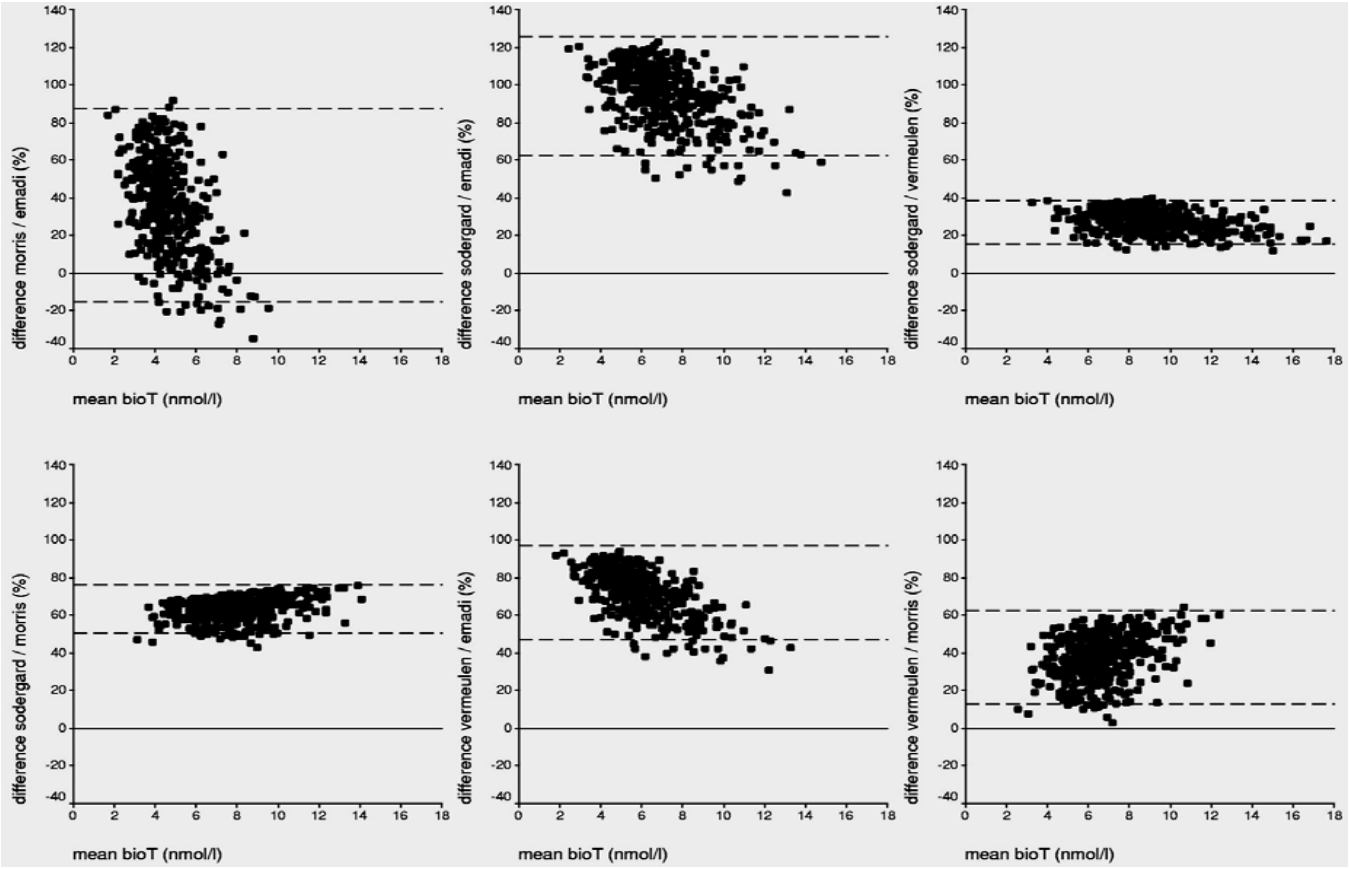
- Sodergard et al. (bioTS and FTS)
- Vermeulen et al. (bioTV and FTV)
- Emadi-Konjin et al. (bioTE)
- Morris et al. (bioTM)
- Ly et al. (FTL)]

Compared to estimate bioT and FT concentrations in samples obtained from 399 independently living men (ages 40–80 years) participating in a cross-sectional, single-center study.

Calculation of Bioavailable and Free Testosterone in Men: A Comparison of 5 Published Algorithms
de Ronde et al, Clin Chem 52: 1777-1784, 2006

- Calculated FT and bioT concentrations, most often obtained with the Vermeulen and the Sodergard methods, are used widely in the endocrinology literature.
- In most publications no arguments are given for the choice of a particular method for calculating FT or bioT although, as described above, choosing a particular set of constants will obviously influence results of calculated free and bioavailable hormone concentrations and thus might influence results of analyses.

Plots of the percentage differences in calculated bioT concentrations against the average of the 2 applied algorithms.
The *solid line* represents 0%, the *dotted lines* the 2 SD of the mean percentage difference.



de Ronde et al, Clin Chem 52: 1777-1784, 2006

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- Algorithms to calculate FT and bioT must be revalidated in the local setting, otherwise over- or underestimation of FT and bioT concentrations can occur.

- Additionally, confounding of the results by SHBG concentrations may be introduced

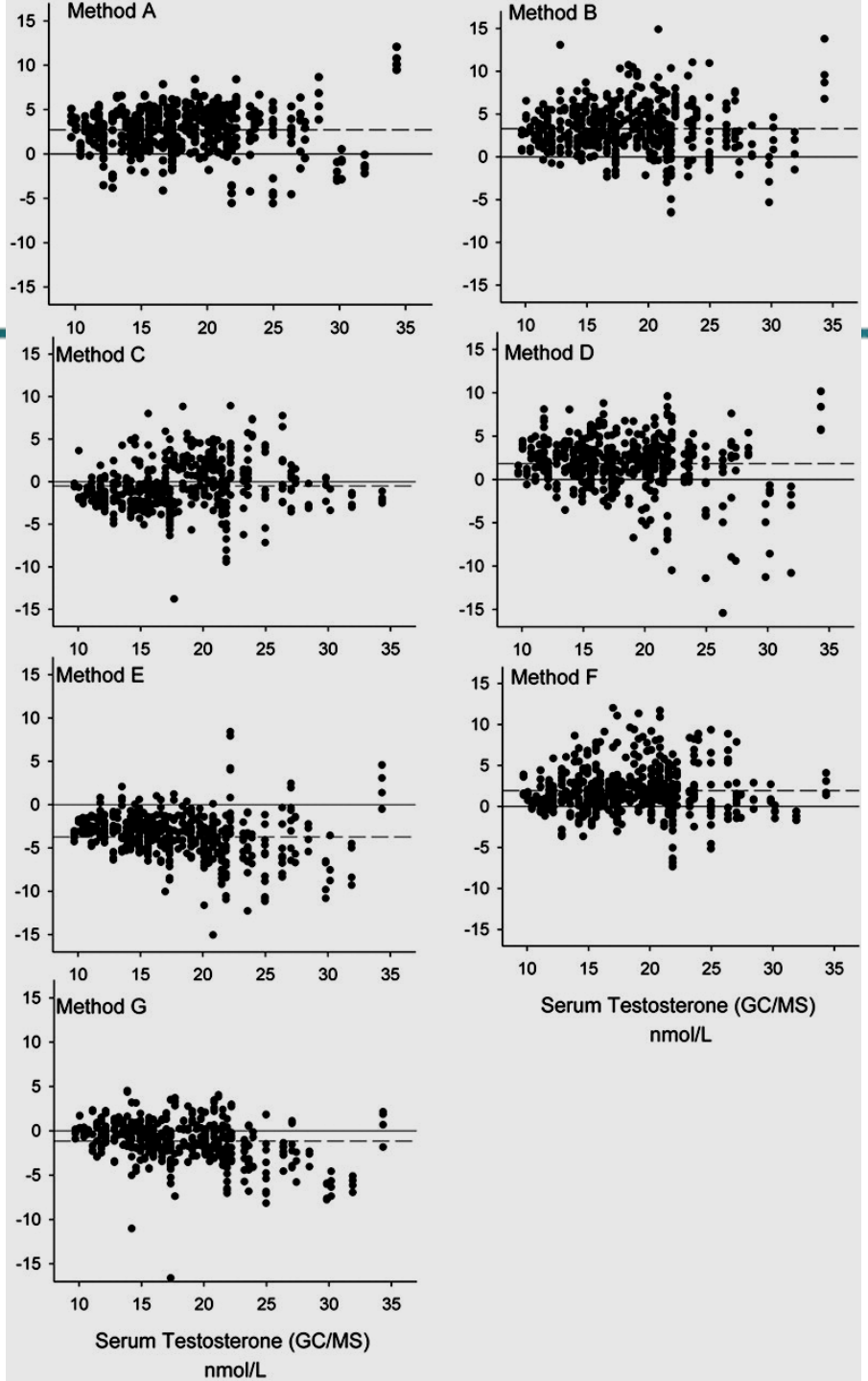


FIG. 1. Deviance plots of the difference between each of the seven methods (A-G) from the reference GC/MS method

Evaluation of Automated Platform Assays

Sikaris, K. et al. J Clin Endocrinol Metab 2005;90:5928-5936

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Utility, Limitations, and Pitfalls in Measuring Testosterone: An Endocrine Society Position Statement

JCEM 92, 405-413, 2007

- TT concentrations in plasma vary over 3 orders of magnitude depending on age, gender, and the presence of disease.
- The concentration of TT varies with time of day.
- Other steroids of similar structure and abundance in the circulation lead to assay interference.
- Only 1–3% of T is not bound to plasma proteins, raising questions about whether TT or free T (FT) is the most clinically useful measure.
- Age- and gender-corrected normal ranges, using a standardized assay, are generally lacking.
- There is no universally recognized T-calibrating standard.

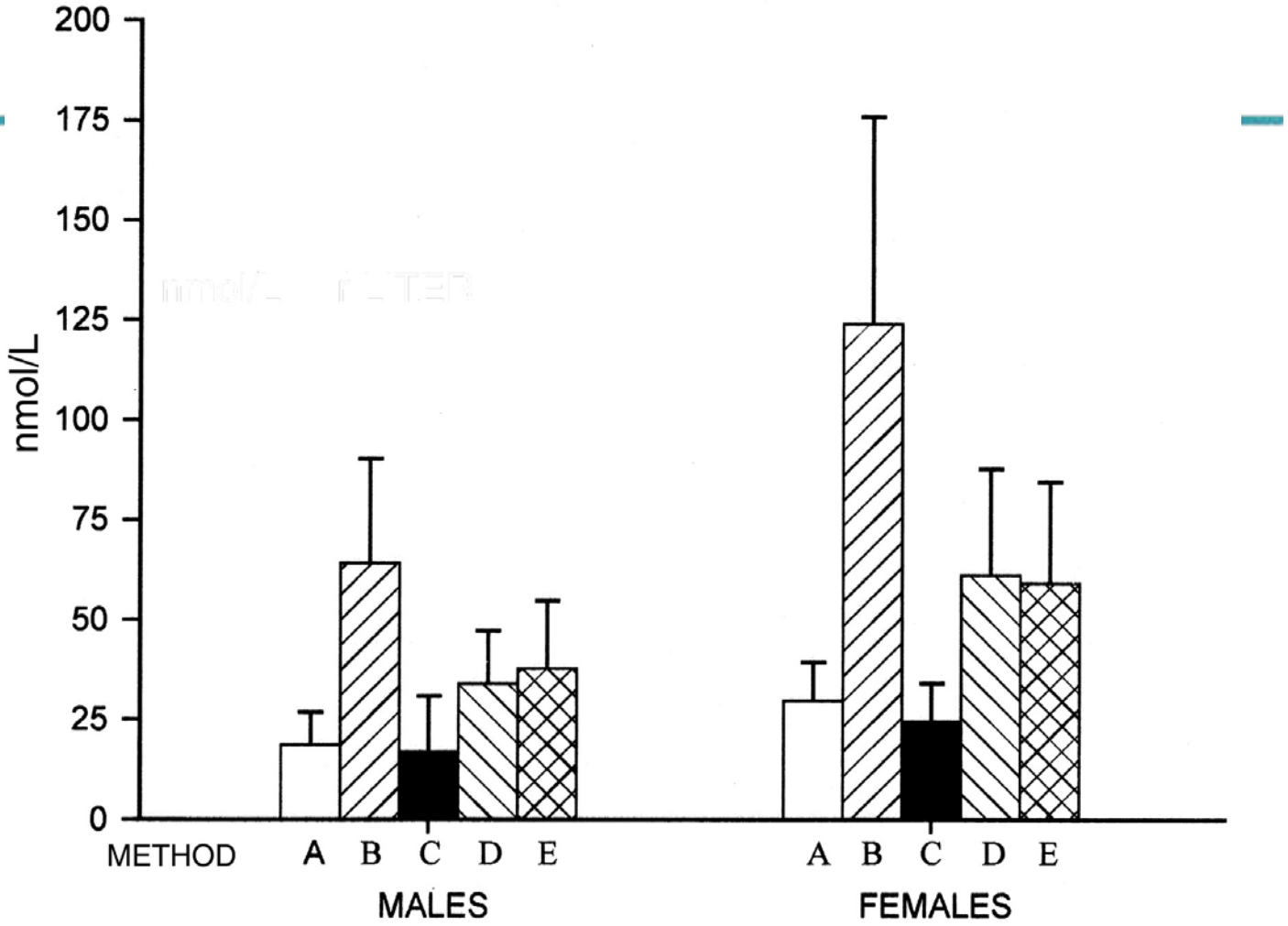
SHBG assay range

	Assay range	Regulatory status
DSL	6, 5 - 300 nmol/L	For Research Use Only within North America
Kupat Holim A	<71	????
Kupat Holim B	≤85	????
Kupat Holim C	No data	
Kupat Holim D	No Need	

Sex Hormone-binding Globulin Concentration: Differences Among Commercially Available Methods

Bukowski et al, Clin Chem 46: 1415-1416, 2000

Mean [+ SD (bars)] SHBG concentrations (nmol/L) as measured in males and females by the respective methods



Free & Bioavailable Testosterone calculator

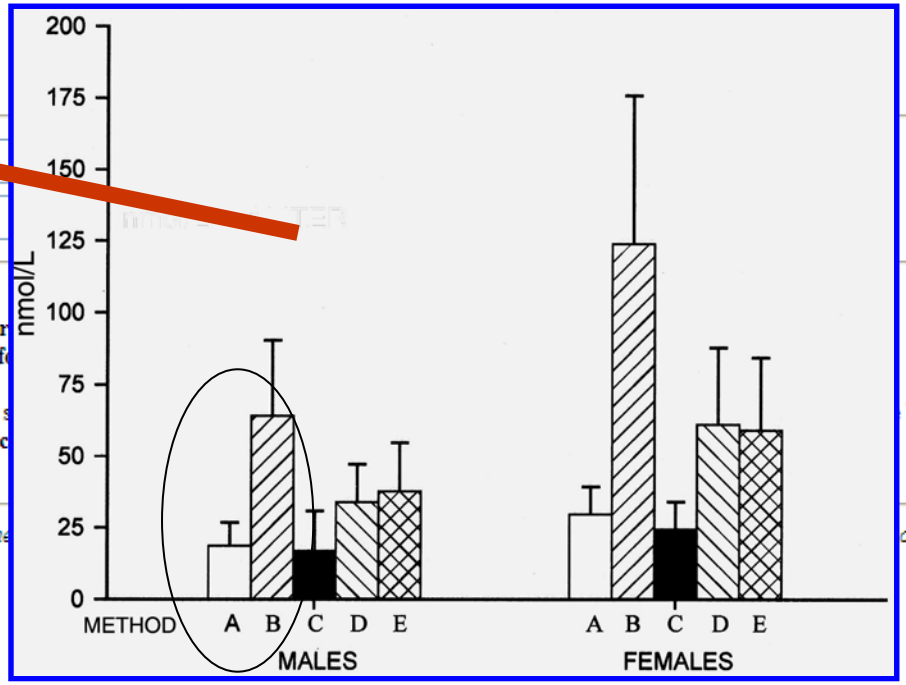
These calculated parameters more accurately reflect the level of bioactive testosterone than does the sole measurement of total serum testosterone. Testosterone and dihydrotestosterone (DHT) circulate in plasma unbound (free approximately 2 - 3%) ,bound to specific plasma proteins (sex hormone-binding globulin SHBG) and weakly bound to nonspecific proteins such as albumin. The SHBG-bound fraction is biologically inactive because of the high binding affinity of SHBG for testosterone. Free testosterone measures the free fraction, bioavailable testosterone includes free plus weakly bound to albumin.

Albumin	43	g/L
SHBG		nmol/L
Testosterone		nmol/L

Calculate

Explanation and examples

Free Testosterone	
Bioavailable Testosterone	



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WARNING! The calculated free and bioavailable testosterone are reliable in most clinical s steroids binding to SHBG; e.g. in women during pregnancy, in men during treatment induc by

This calculator was developed at the Hormonology department, University Hospital of Ghe or *help contact us Dr. Tom Fiers or Prof. Dr. J.M. Kaufman*

Why????????

- SHBG exists in several forms in the blood, in part because of differences in glycosylation.
- Antibodies raised to SHBG may recognize these forms differently, and thus different antibodies could give disparate results in an immunoassay.
- Although human SHBG was always the antigen, the antibodies were raised in different species, and this could produce antibodies that recognize SHBG differently.
- The preparation of the antigens could differ and produce antibodies that recognize SHBG in dissimilar manner

Bukowski, C. et al. Clin Chem 2000;46:1415-1416

Metabolic Syndrome

Abdominal Obesity
Visceral Fat

Insulin Resistance

Hyperglycemia

Hypertension

Dyslipidemia

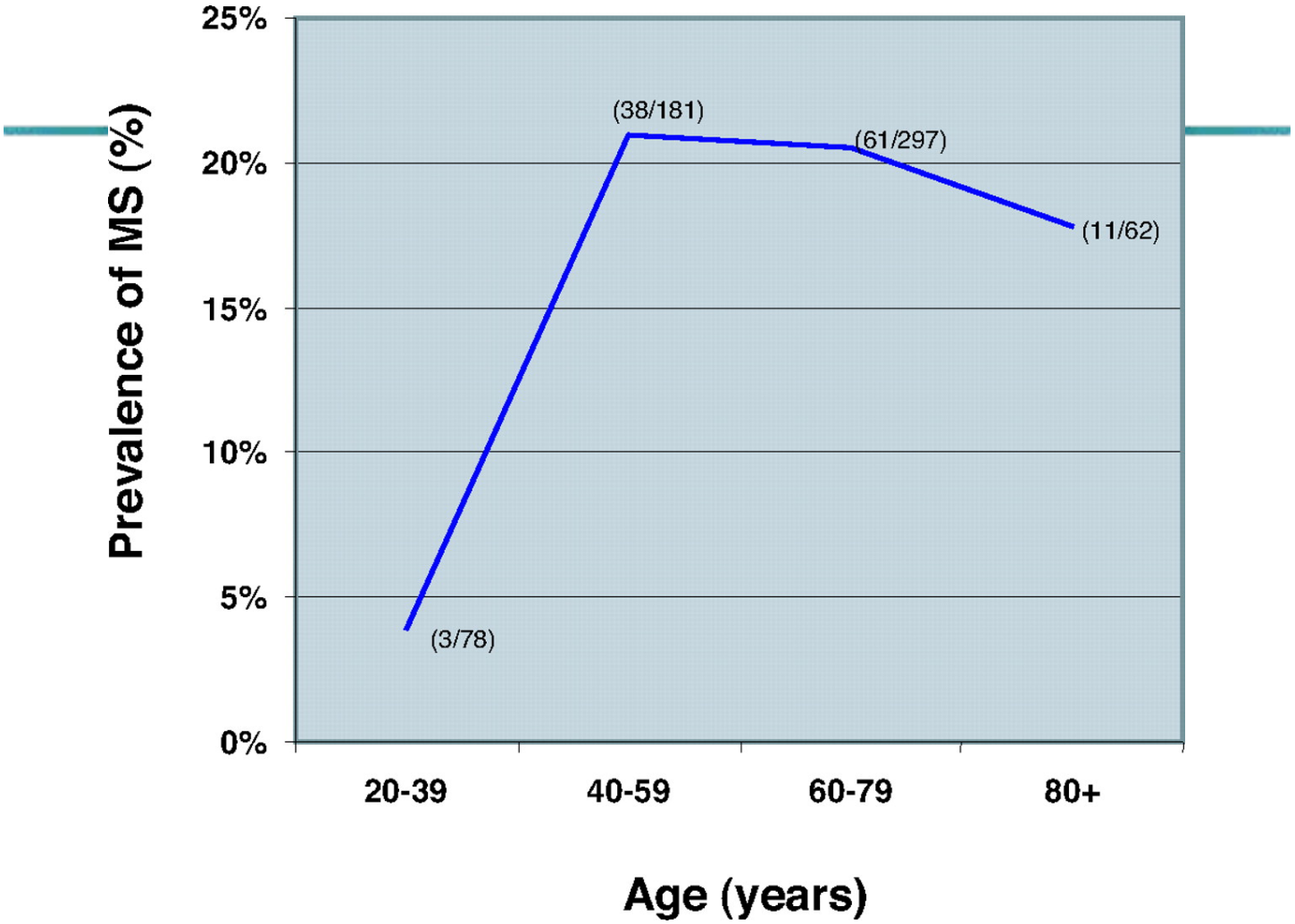
Atherosclerosis

Metabolic Syndrome Develops Rapidly in GnRH-analog treated Prostate Cancer Patients

Androgen deprivation therapy

- Increases obesity
- Decreases insulin sensitivity
- Adversely alters lipid profiles
- May be associated with a greater incidence of diabetes and cardiovascular disease.

Prevalence of the MS as a function of age in BLSA men at entry



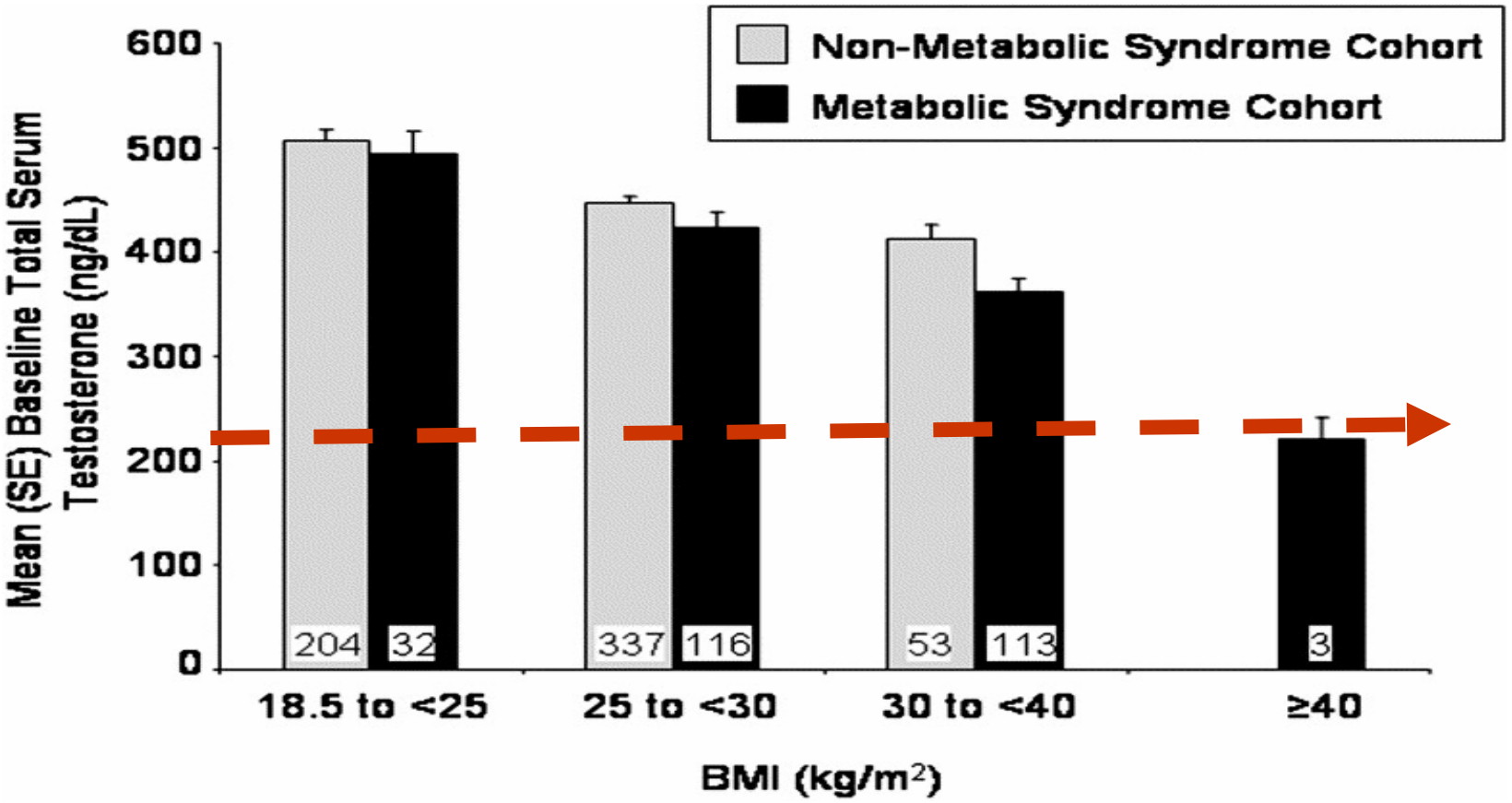
Rodriguez, A. et al. J Clin Endocrinol Metab 2007;92:3568-3572

The Journal of Clinical Endocrinology & Metabolism

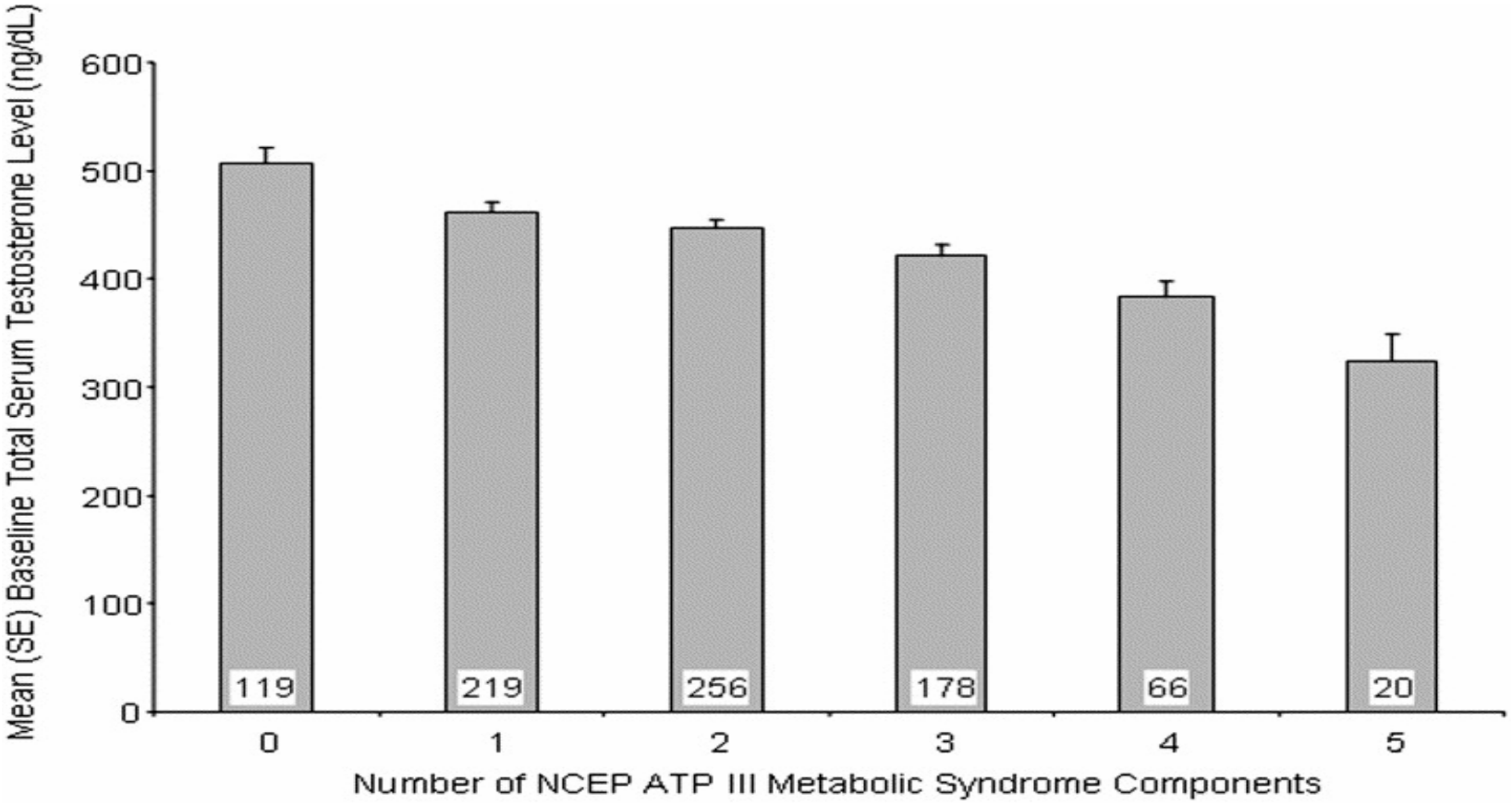
The Metabolic Syndrome and Testosterone in Men

- Evidence for cross-sectional relationship
- Evidence for prediction in longitudinal studies
- Evidence for induction of MS following rapid de-androgenization
- Evidence for reversal of Metabolic syndrome or its components with testosterone replacement therapy

Relationship among total serum testosterone, BMI and metabolic syndrome .

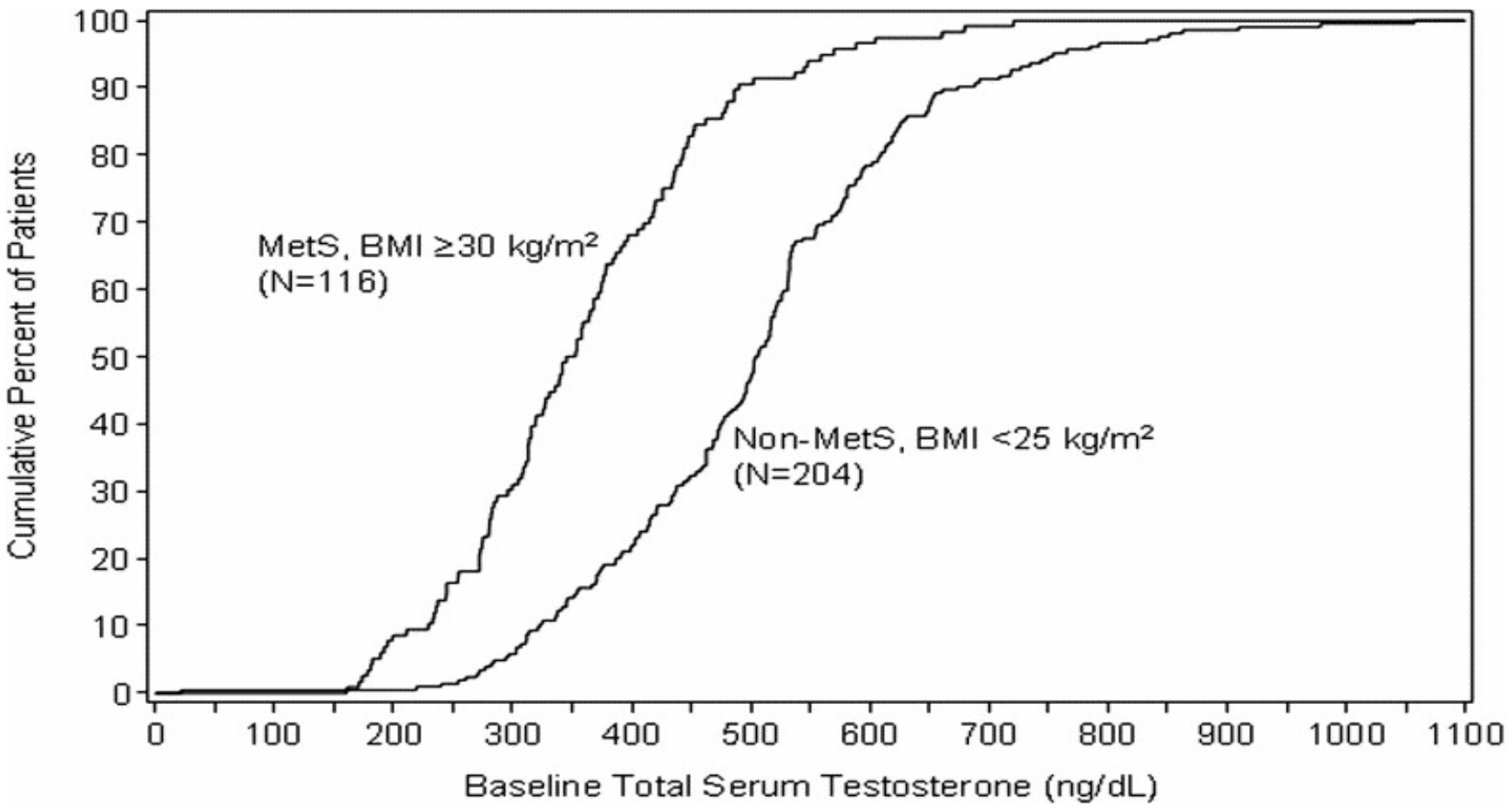


Mean baseline total serum testosterone levels among patients with none, 1, 2, 3, 4 or all 5 of NCEP ATP III metabolic syndrome components .



Kaplan et al, J urol 176:1524, 2006

Cumulative percent population baseline total serum testosterone distribution curves for lean men (BMI less than 25 kg/m (without MetS vs obese men (BMI 30 kg/m or greater) with MetS .



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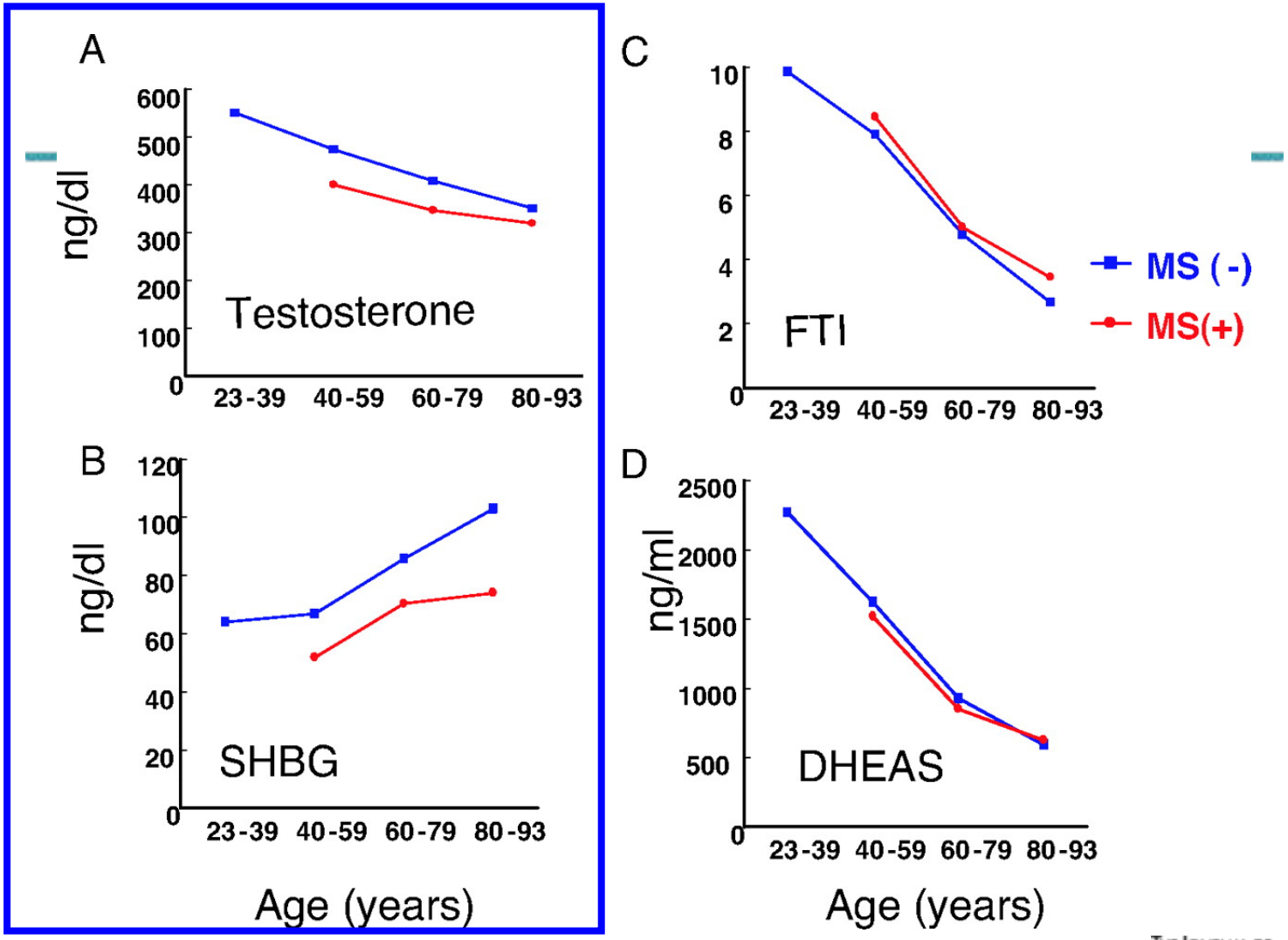
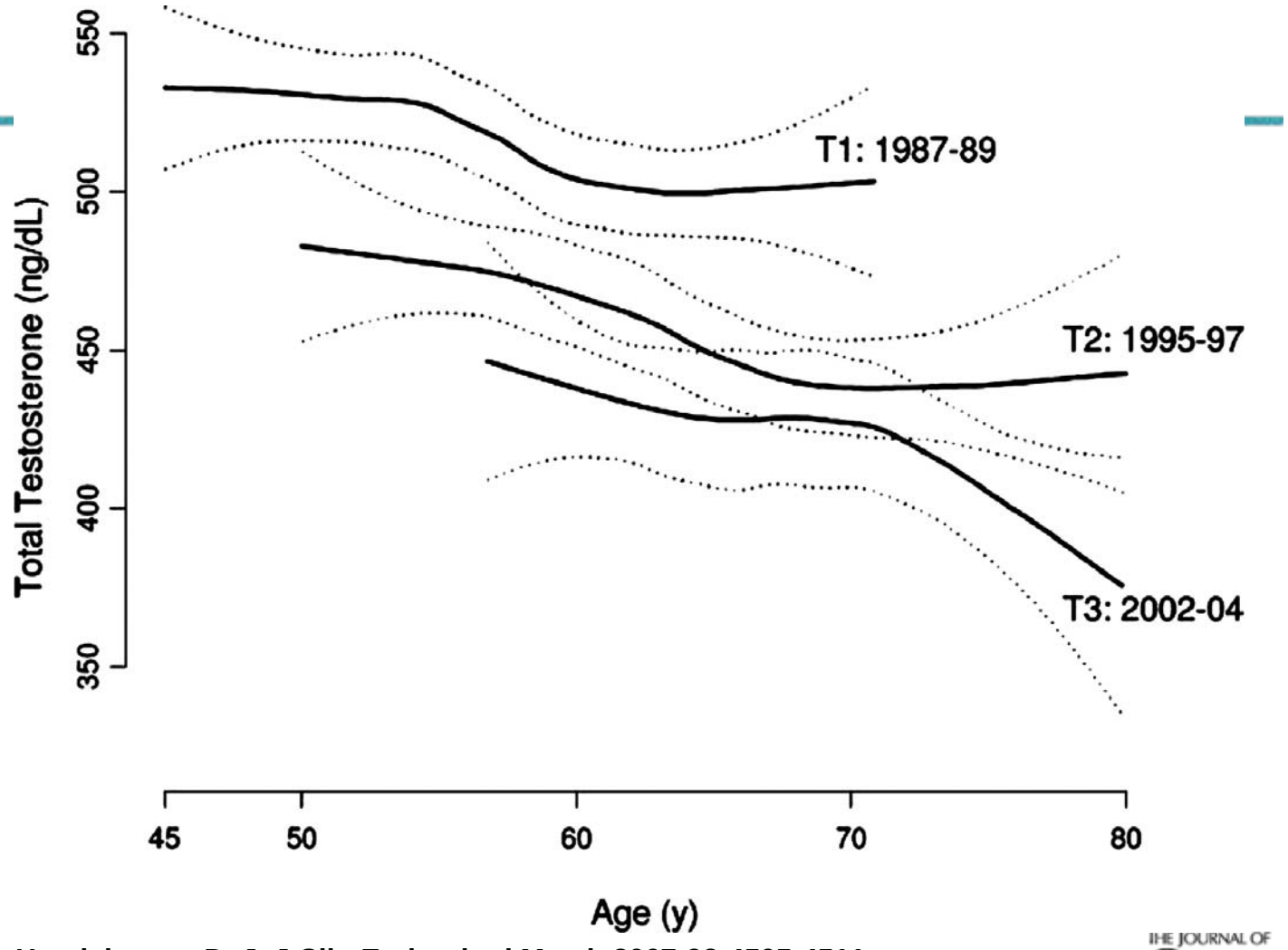
Androgen levels in men stratified by age and the presence or absence of the MS at entry



Rodriguez, A. et al. J Clin Endocrinol Metab 2007;92:3568-3572

The Journal of Clinical Endocrinology & Metabolism

. Crude mean total T concentrations by Massachusetts Male Aging Study study wave (T1, T2, T3) with confidence bands (dotted lines)



Handelsman, D. J. J Clin Endocrinol Metab 2007;92:4505-4511

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Association of Endogenous Sex Hormones With Diabetes and Impaired Fasting Glucose in Men
Multi-Ethnic Study of Atherosclerosis

Colangelo et al, *Diabetes Care 2009; 32 : 1049-1051*

- *
- OBJECTIVE To assess associations of sex hormones with impaired fasting glucose (IFG) and type 2 diabetes in men.
- RESEARCH DESIGN AND METHODS A total of 3,156 African American, Non-Hispanic white, Hispanic, and Chinese-American men aged 45–84 years who participated in the baseline visit of the Multi-Ethnic Study of Atherosclerosis (MESA) were included. Oddsratios and95% CIs for type 2 diabetes and IFG compared with normal fasting glucose for quartiles of hormones were estimated.

Association of Endogenous Sex Hormones With Diabetes andImpaired Fasting Glucose in Men
Multi-Ethnic Study of Atherosclerosis
Colangelo et al, *Diabetes Care 2009; 32 : 1049-1051*

- RESULTS After adjusting for age, ethnicity, BMI, and waist circumference, IFG and diabetes were associated inversely with total testosterone and sex hormone–binding globulin (SHBG) and positively with estradiol (E2). Dehydroepiandrosterone was positively associated with IFG but not with diabetes. Associations did not differ across ethnic groups.

- CONCLUSIONS Regardless of obesity, total testosterone and SHBG were associated inversely and E2 was associated positively with IFG and diabetes in men.

Establishing the MS/T relation prospectively

TABLE 4. Development of the MS (ATPIII) in subjects without the MS or DM at baseline: best three proportional hazards regression models by number of variables in the model (n = 417)

No. of variables	χ^2	Variables included in model
1	72.02	BMI
1	19.45	SHBG
1	17.21	Total T
2	77.09	BMI, SHBG
2	75.11	BMI, total T
2	74.69	BMI, FTI
3	83.75	BMI, total T, FTI
3	80.62	BMI, total T, SHBG
3	80.38	Age, BMI, FTI
4	85.84	Age, BMI, total T, FTI
4	83.82	BMI, total T, SHBG, FTI
4	81.85	Age, BMI, SHBG, FTI
5	85.91	Age, BMI, total T, SHBG, FTI

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

Kupelian et al, JCEM 91:843-850, 2006

- Data were obtained from the Massachusetts Male Aging Study, a population-based prospective cohort of 1709 men observed at three time points (T1, 1987-1989; T2, 1995-1997; T3, 2002-2004).
- MetS was defined using a modification of the ATP III guidelines.
- Clinical androgen deficiency (AD) was defined using a combination of testosterone levels and clinical signs and symptoms.
- Analysis was conducted in 950 men without MetS at T1

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

Kupelian et al, JCEM 91:843-850, 2006

- Lower levels of total testosterone and SHBG were predictive of MetS, particularly among men with a body mass index (BMI) below 25 kg/m2 with adjusted RRs for a decrease in 1 sd of 1.41 and 1.65.

- Results were similar for the AD and MetS association, with RRs of 2.51 among men with a BMI less than 25 compared with an RR of 1.22 in men with a BMI of 25 or greater.

- 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.

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

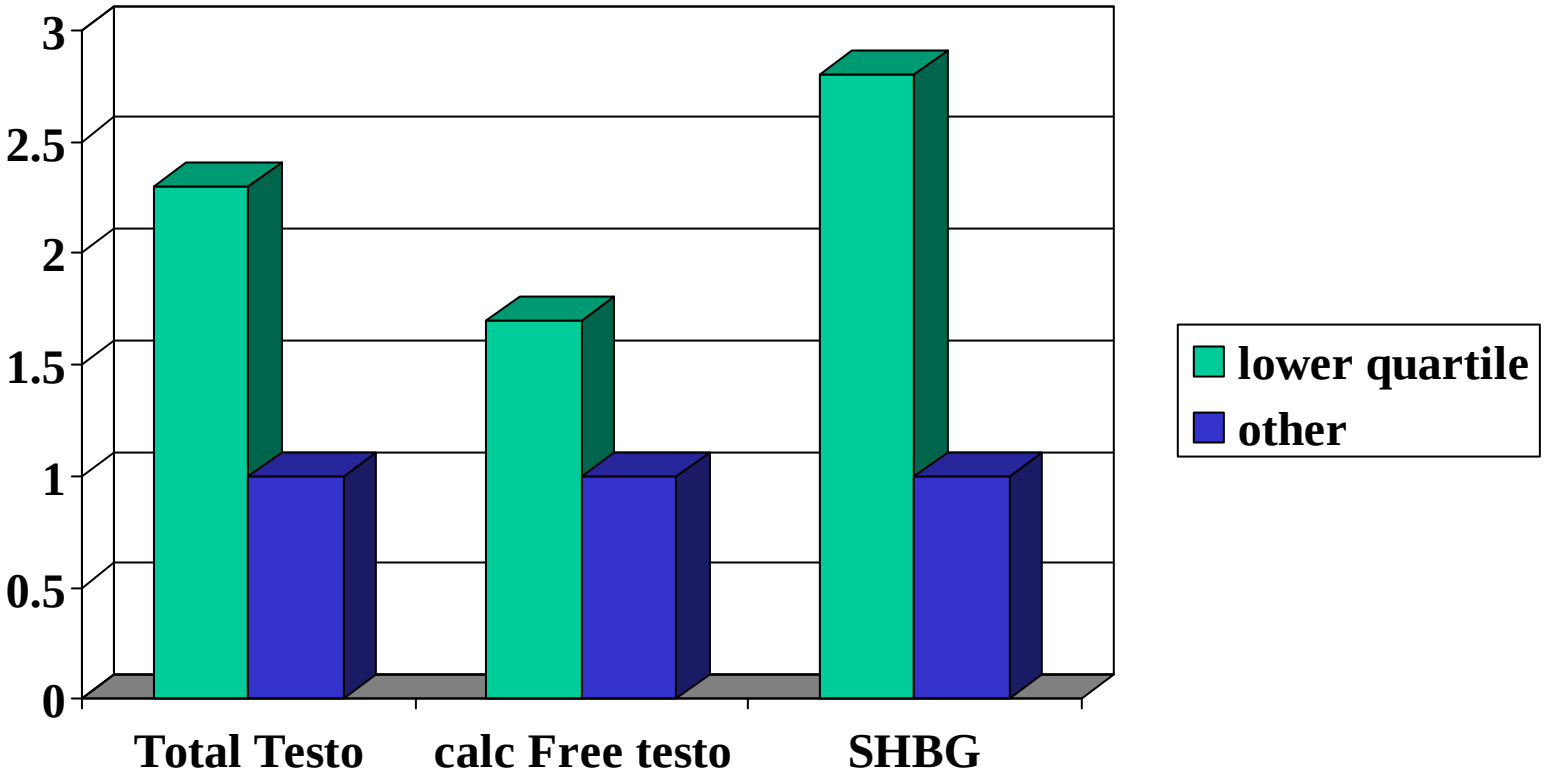
Laaksonen et al, Diabetes Care 2004 ;. 27: 1036-1041

- 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

- After 11 years of follow-up, 147 men had developed the metabolic syndrome (National Cholesterol Education Program criteria) and 57 men diabetes.

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

Laaksonen et al, Diabetes Care 2004 ;. 27: 1036-1041



OR for the development of MS in the course of 11 yrs

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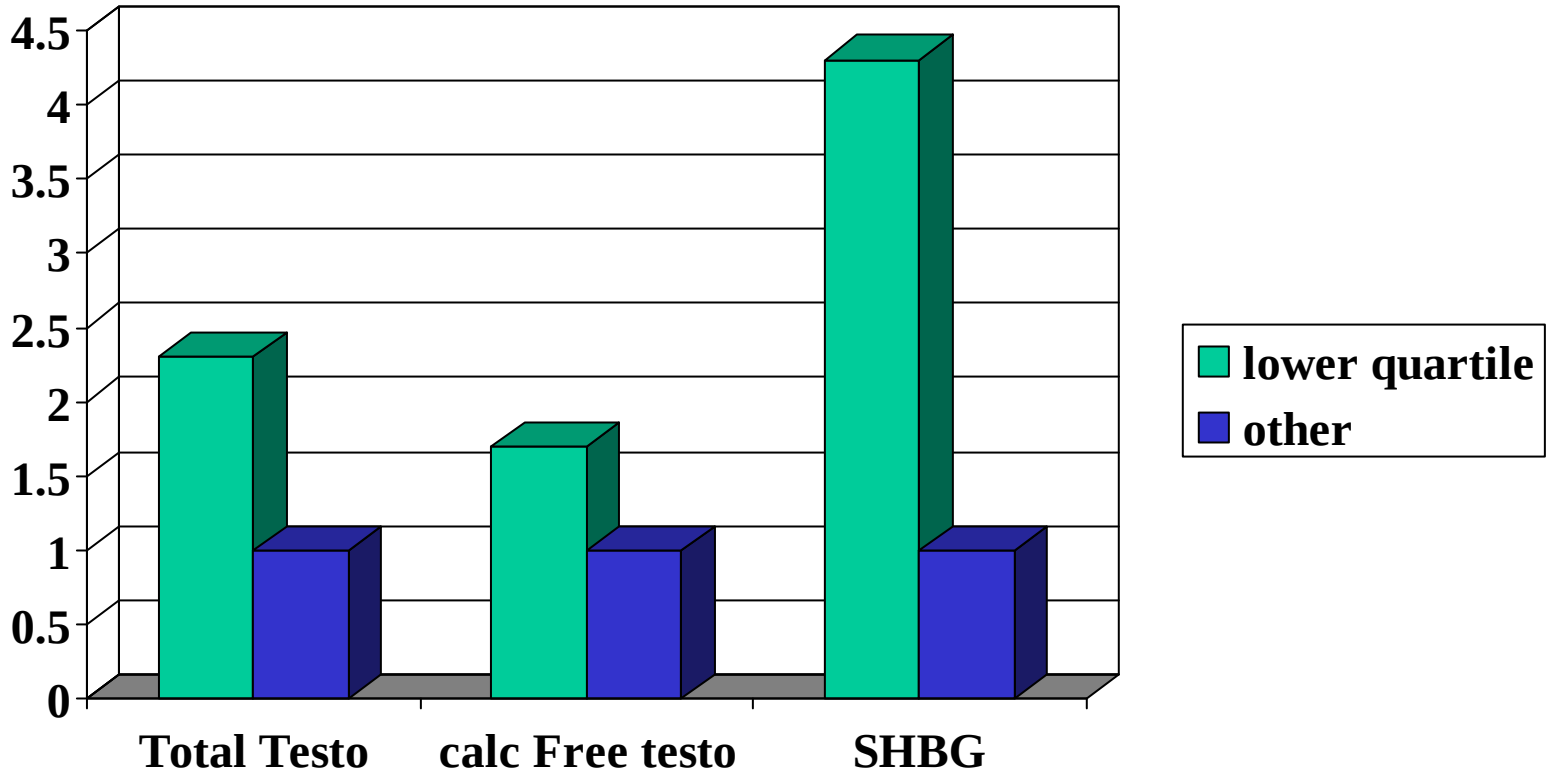


OR for the development of Diabetes in the course of 11 yrs

Table 3. Risk of Type 2 Diabetes among Women and Men, According to Sex Hormone–Binding Globulin (SHBG) Level.*

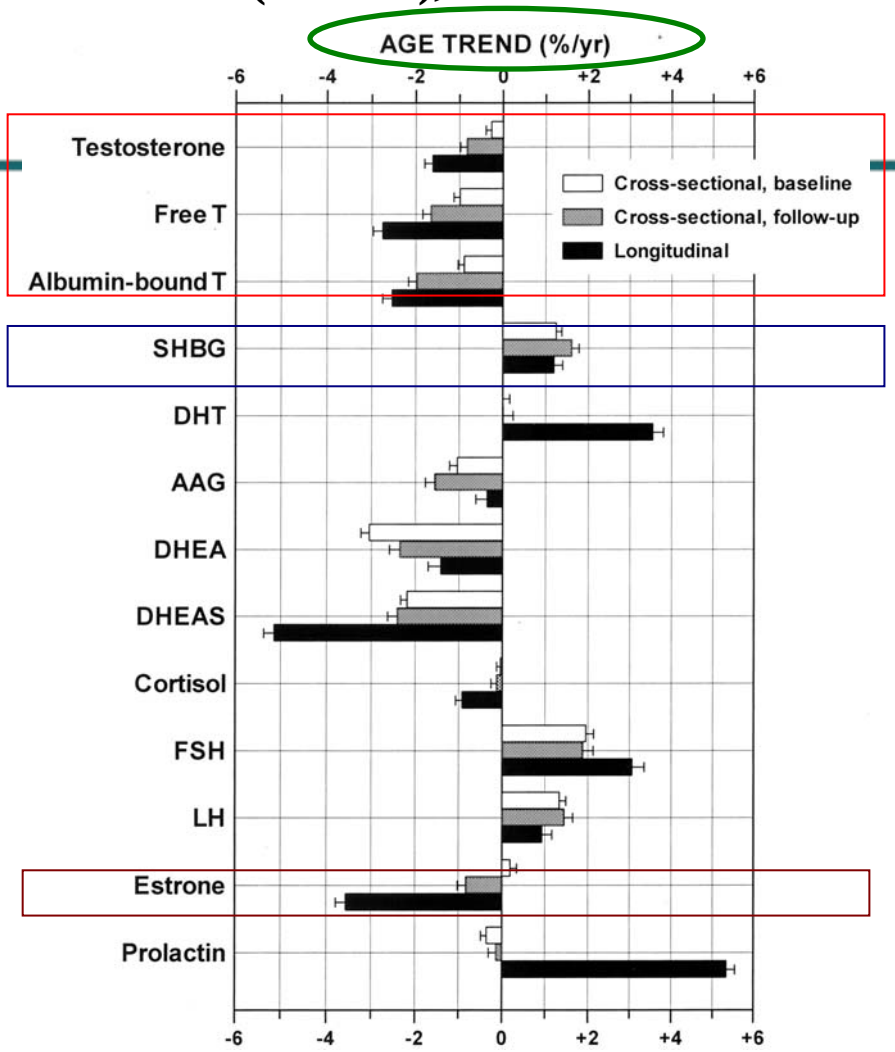
Variable	SHGB Quartile				P Value for Trend
	1 (lowest)	2	3	4 (highest)	
Women					
Median SHBG level — nmol/liter (range)	17.1 (5.8–24.7)	29.3 (24.8–34.6)	39.0 (34.7–44.3)	55.8 (44.4–122)	
No. of participants — case patients/controls†	267/91	49/88	19/89	24/89	
Simple model 1 — odds ratio (95% CI)	1.00	0.26 (0.11–0.33)	0.08 (0.04–0.16)	0.12 (0.05–0.25)	<0.001
Multivariable model 2 — odds ratio (95% CI)	1.00	0.16 (0.08–0.33)	0.04 (0.01–0.12)	0.09 (0.03–0.21)	<0.001
Sensitivity model — odds ratio (95% CI)					
Multivariable + reproductive and sociologic covariates	1.00	0.11 (0.05–0.24)	0.03 (0.01–0.10)	0.08 (0.02–0.27)	<0.001
Multivariable + waist circumference	1.00	0.16 (0.07–0.34)	0.04 (0.01–0.12)	0.09 (0.03–0.23)	<0.001
Multivariable + C-reactive protein	1.00	0.18 (0.08–0.39)	0.05 (0.01–0.14)	0.11 (0.04–0.27)	<0.001
Multivariable + fasting LDL and HDL cholesterol and triglycerides	1.00	0.22 (0.09–0.51)	0.06 (0.02–0.24)	0.16 (0.06–0.45)	<0.001
Multivariable + glycated hemoglobin	1.00	0.22 (0.09–0.50)	0.06 (0.02–0.19)	0.12 (0.04–0.37)	<0.001
Multivariable (excluding first 3 yr of follow-up)	1.00	0.16 (0.06–0.38)	0.04 (0.01–0.12)	0.06 (0.02–0.19)	<0.001
Men					
Median SHBG level — nmol/liter (range)	15.2 (4.4–19.4)	22.2 (19.4–25.7)	29.7 (25.8–33.9)	38.0 (34.2–75.7)	
No. of participants — case patients/controls	92/43	47/42	24/43	7/42	
Simple model 1 — odds ratio (95% CI)	1.00	0.62 (0.31–1.23)	0.36 (0.16–0.82)	0.11 (0.03–0.37)	<0.001
Multivariable model 2 — odds ratio (95% CI)	1.00	0.48 (0.22–1.03)	0.41 (0.15–1.14)	0.10 (0.03–0.36)	<0.001
Sensitivity model — odds ratio (95% CI)					
Multivariable + glycated hemoglobin	1.00	0.39 (0.08–1.97)	0.21 (0.01–3.37)	0.10 (0.01–0.75)	0.02
Multivariable (excluding first 2 yr of follow-up)	1.00	0.63 (0.26–1.53)	0.38 (0.11–1.37)	0.08 (0.01–0.69)	<0.001

Testosterone, estradiol, SHBG and the risk of type 2 DM in men

- Low testosterone levels were associated with higher risk of type 2 diabetes among men
- Low plasma levels of SHBG were weakly associated with type 2 diabetes in men
- Endogenous estradiol levels may be elevated both in men and in postmenopausal women with type 2 diabetes.

Age and Obesity Exert Differential Effects on Sex- Hormones

Cross-sectional and longitudinal trends of T, other androgens and metabolites, and related hormones in middle-aged men, participants in Massachusetts Male Aging Study (MMAS), 1987–97.

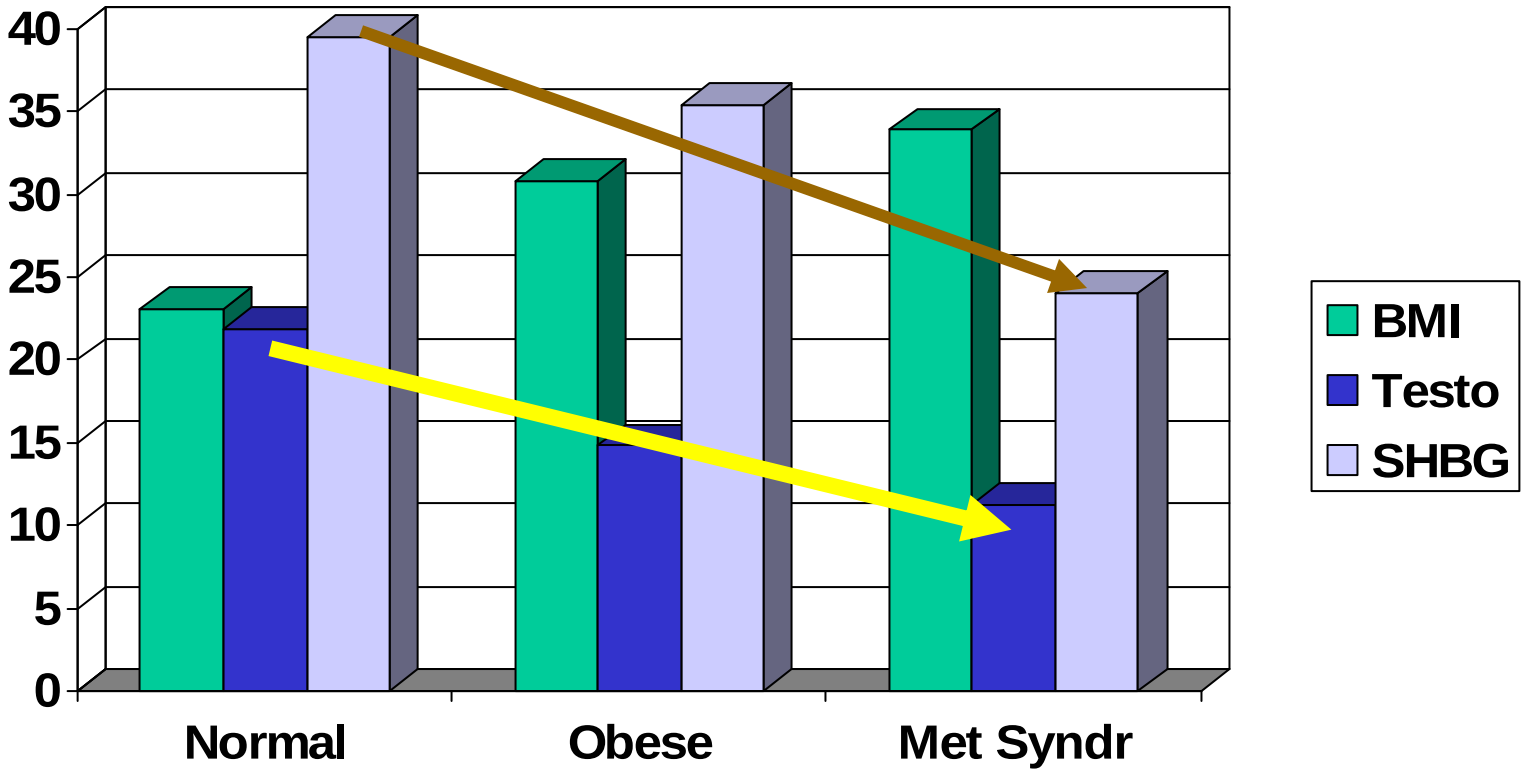


Feldman, H. A. et al. J Clin Endocrinol Metab 2002;87:589-598

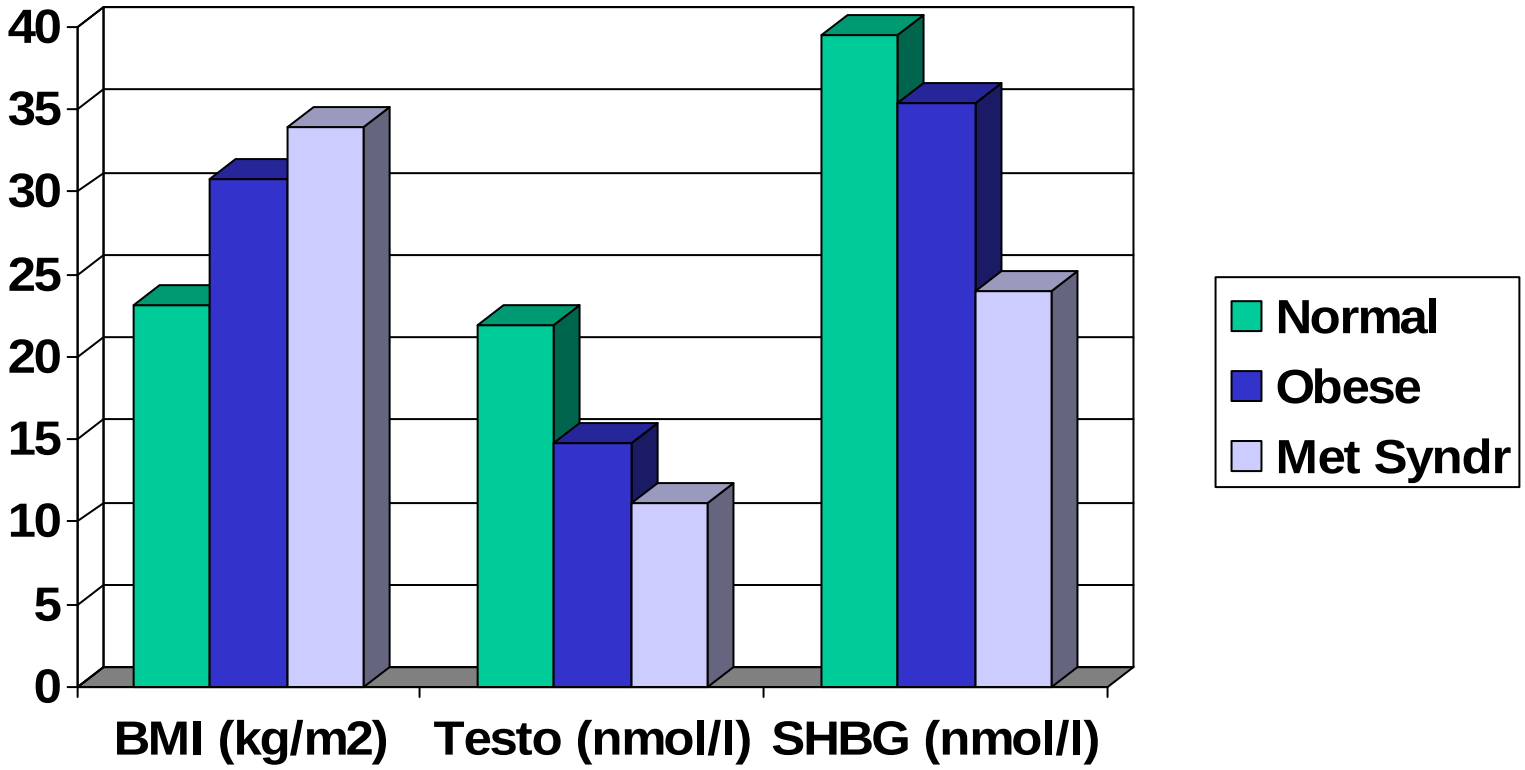
THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Lower serum testosterone is independently associated with insulin resistance in non-diabetic older men: the Health In Men Study./ Yeap et al Eur J Endocrinol. 2009 Oct;161:591

- Cross-sectional analysis of 2470 community-dwelling non-diabetic men aged > or = 70 years.

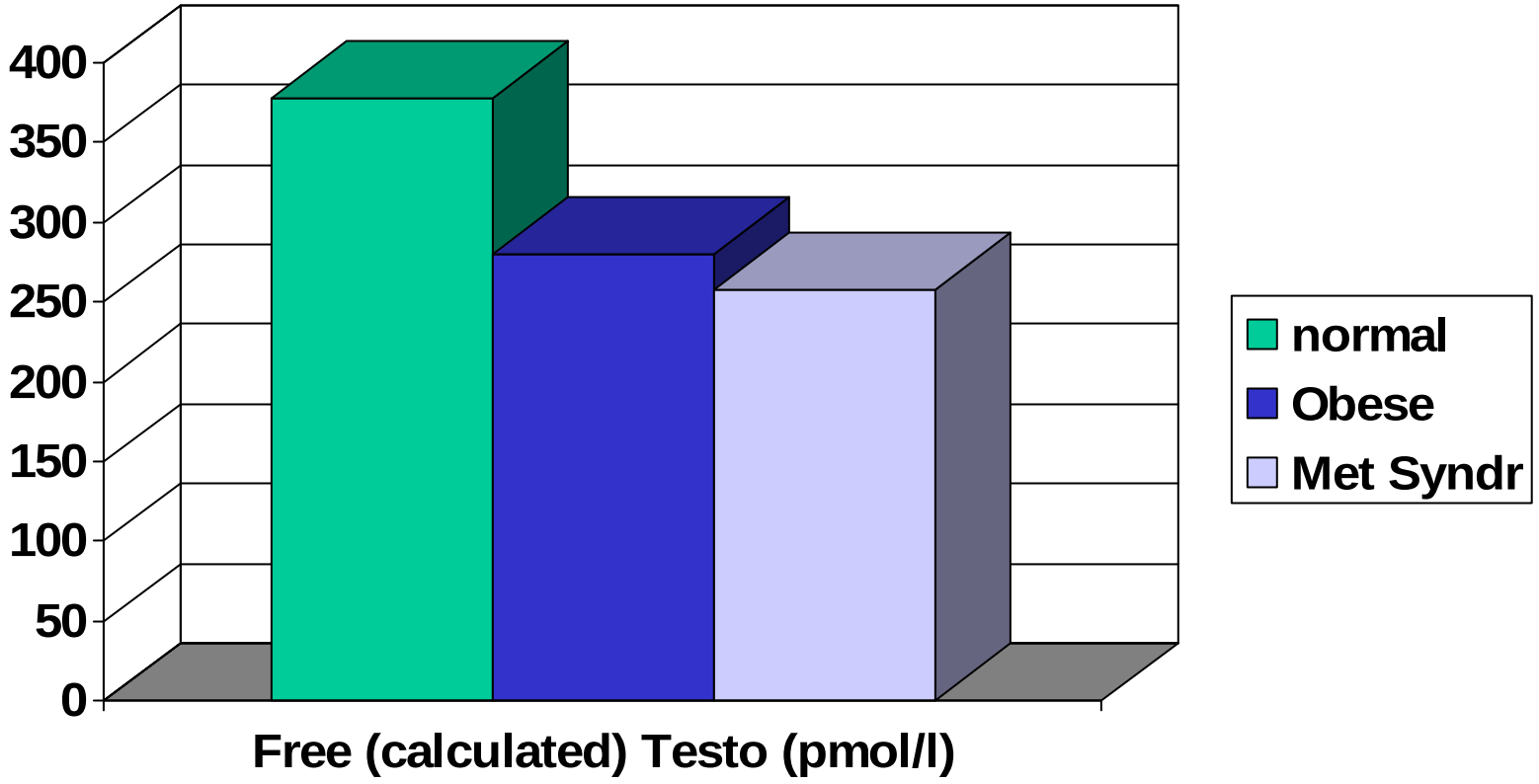

40
35
30
25
20
15
10
5
0
Normal
Obese
Met Syndr
BMI
Testo
SHBG

Testosterone and obesity in men under the age of 40 years



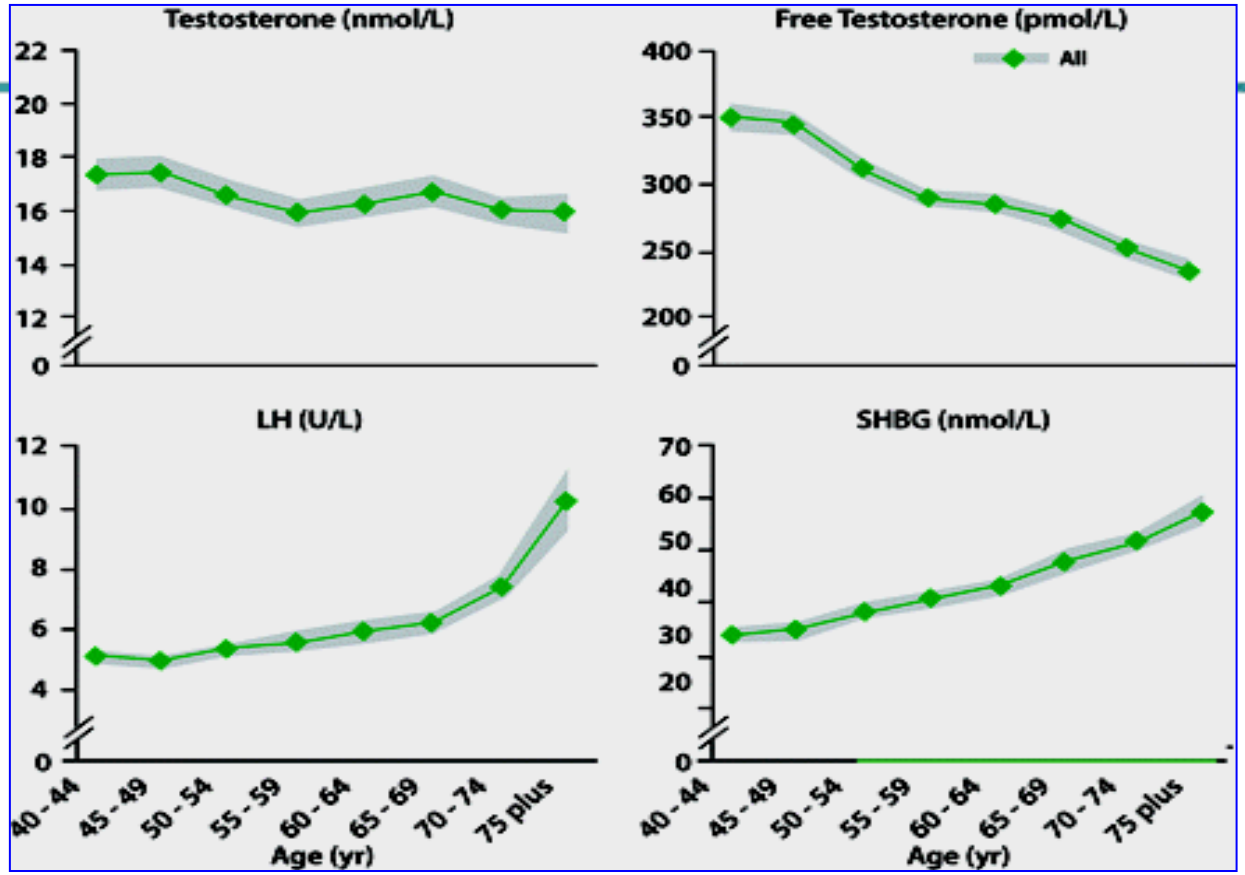
Goncharov et al, Andrologia 41, 76–83

Testosterone and obesity in men under the age of 40 years



Goncharov et al, Andrologia 41, 76–83

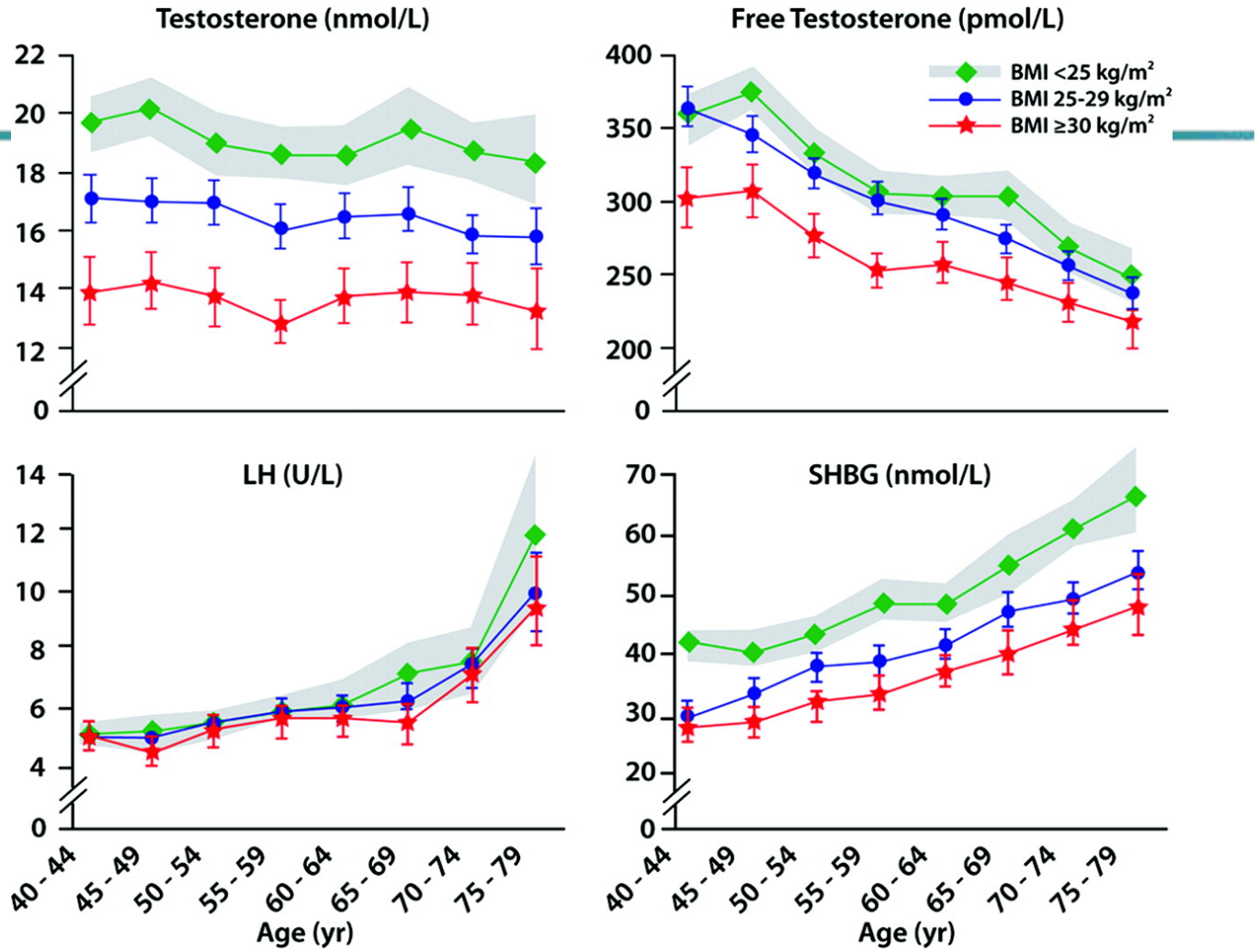
The European Male Aging Study



Cross-sectional survey on 3200 community-dwelling men aged 40–79 yr from a prospective cohort study in eight European countries.

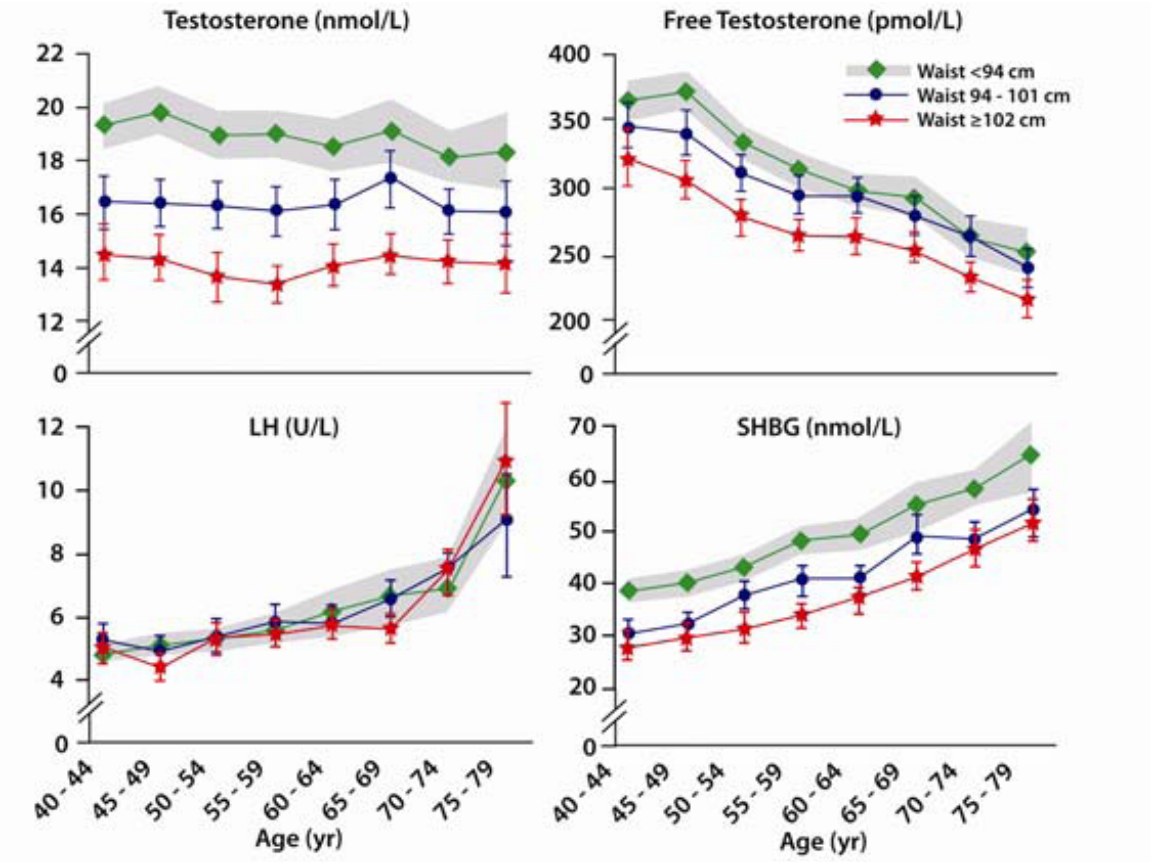
JCEM 93: 2737-2745, 2008

FIG. 2. Relationship between age, BMI, and hormones



Wu, F. C. W. et al. J Clin Endocrinol Metab 2008;93:2737-2745

The Journal of Clinical Endocrinology & Metabolism



Wu, F. C. W. et al. J Clin Endocrinol Metab 2008;93:2737-2745

Treating as a means to evaluate the relationship between the MS and testosterone:

Modifying obesity or modifying andogen deficiency

Effect of Weight Loss On Androgens in Obese Men

- Outpatient supplemented fasting program (320 kcal/day) for 8-20 weeks
- Weight loss (mean, 19.5 kg) were associated with normalization of all the measured parameters
- The mean E1 decreased from 100 +/- 7 to 48 +/- 23 pg/ml
- E2 decreased from 36 +/- 3 pg/ml to 28 +/- 2.1 pg/ml.
- T increased from 400 +/- 20 to 536 +/- 35 ng/dl.
- Data on men remaining on the program for 16 or 20 weeks showed a continued fall of estrogens and stabilization of T and %FT.
- SHBG did not change significantly over the entire time period.

Stanik & Korenman J Clin Endocrinol Metab. 1981;53:828

First International Journal of Andrology
ANDROLOGIA

ORIGINAL ARTICLE

Concurrent improvement of the metabolic syndrome and lower urinary tract symptoms upon normalisation of plasma testosterone levels in hypogonadal elderly men

A. Haider[1], L. J. Gooren[2], P. Padungtod[3] & F. Saad[4,5]

1 Private Urology Praxis, Bremerhaven, Germany;
2 Endocrinology, VUMC, Amsterdam, The Netherlands;
3 Faculty of Veterinary Medicine, Chiang Mai University, Chiang Mai, Thailand;
4 Bayer Schering Pharma, Scientific Affairs Men's Healthcare, Berlin, Germany;
5 Gulf Medical University School of Medicine, Ajman, UAE

Andrologia **41**, 7–13 2009

A large cohort of 95 middle-aged to elderly hypogonadal men (T levels 5.9–12.1 nmol l)1) were treated with parenteral testosterone undecanoate and its effects on the metabolic syndrome {waist circumference, cholesterol, CRP and LUTS [residual bladder volume (RBV), International Prostate Symptoms Score (IPSS), prostate volume, prostate-specific antigen (PSA)]}

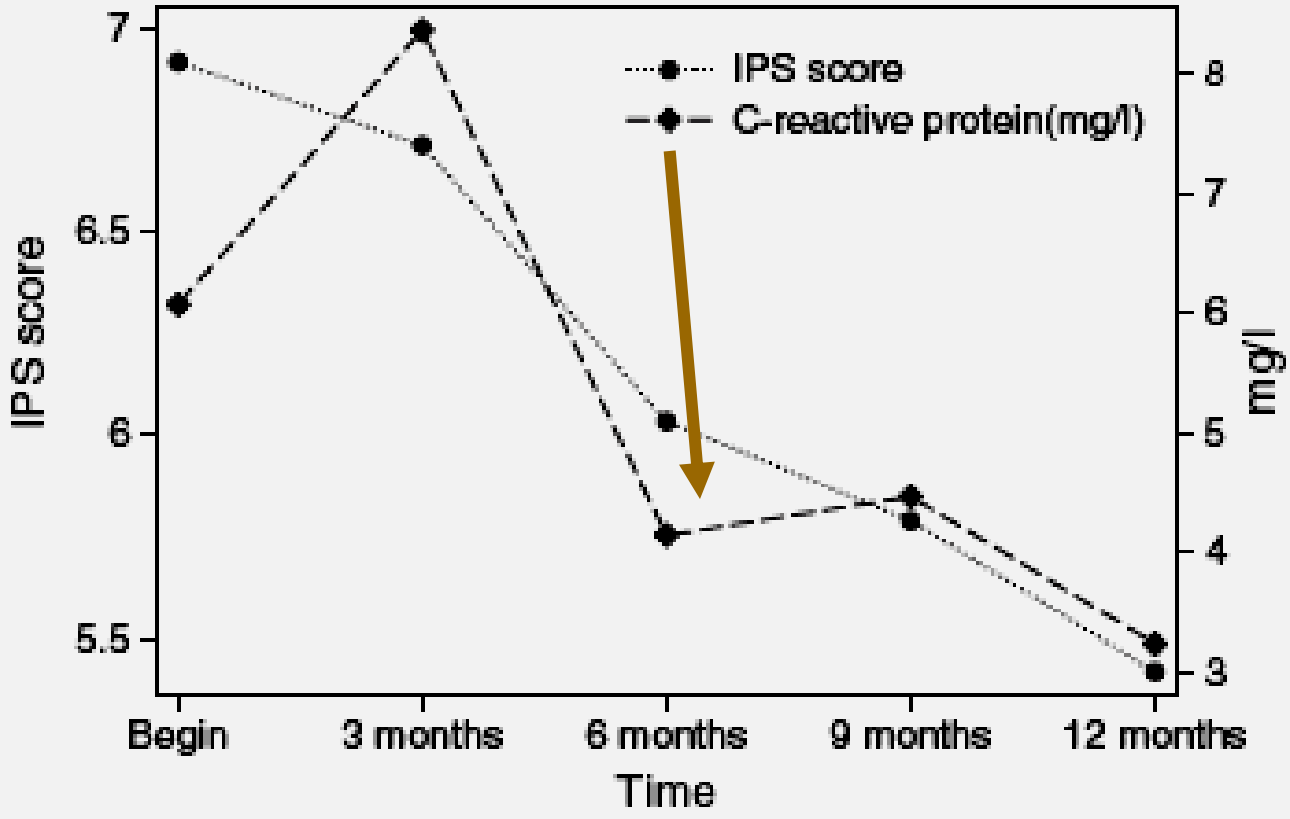


Fig. 2 Mean of C-reactive protein and International Prostate Symptom Score (IPSS) over the study period in 117 men receiving treatment with testosterone undecanoate.

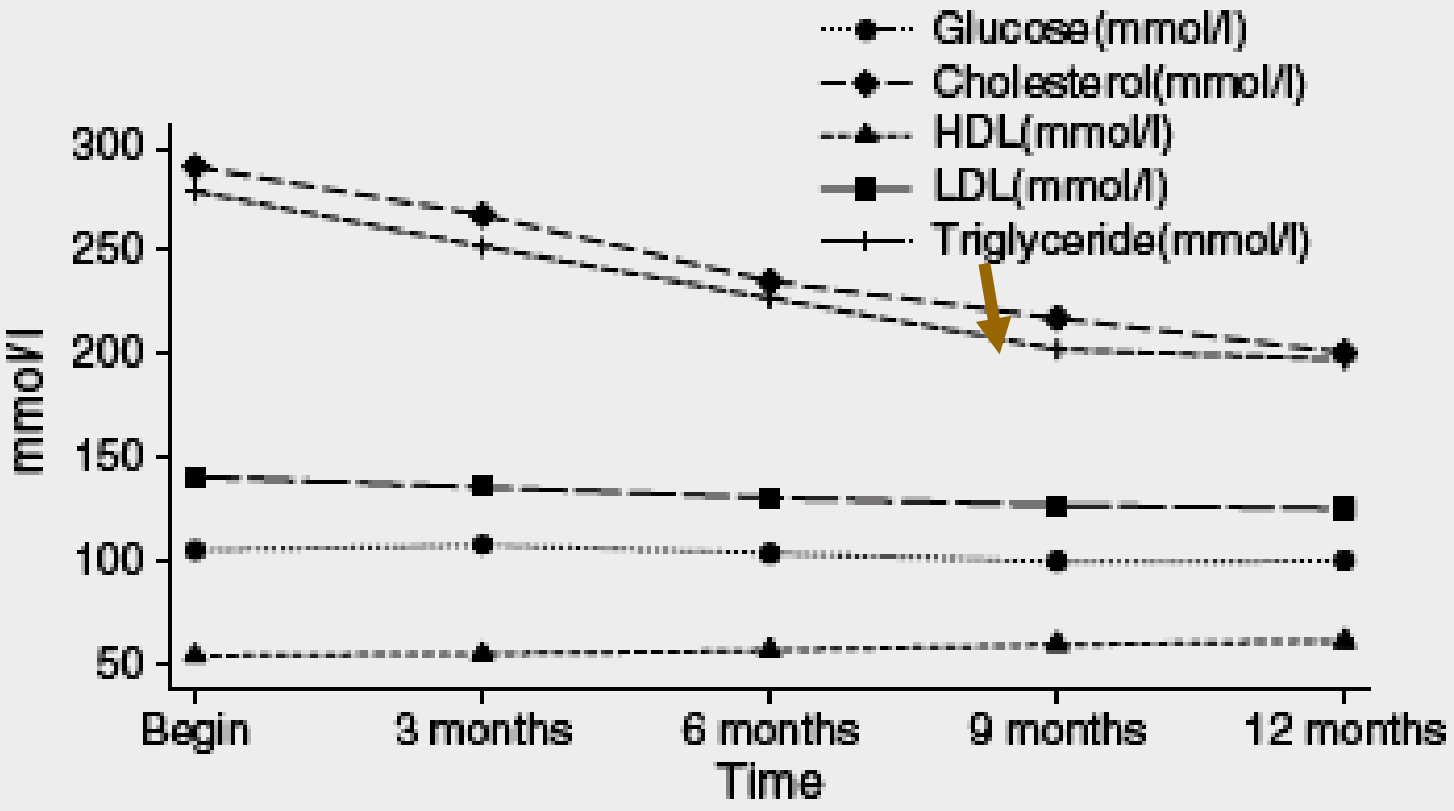


Fig. 1 Mean of metabolic parameters over the study period in 117 men receiving treatment with testosterone undecanoate.

Journal of Andrology, Vol. 30, No. 6, November/December 2009

Fifty-two–Week Treatment With Diet and Exercise Plus Transdermal Testosterone Reverses the Metabolic Syndrome and Improves Glycemic Control in Men With Newly Diagnosed Type 2 Diabetes and Subnormal Plasma Testosterone

ARMIN E. HEUFELDER,* FARID SAAD,†‡ MATHIJS C. BUNCK,§ AND LOUIS GOOREN§

*From †Business Unit Primary Care, Men's Healthcare, Scientific Affairs, Bayer Schering Pharma AG, Berlin, Germany; ‡Gulf Medical University, Ajman, United Arab Emirates; and the §Department of Endocrinology, Vrije University Medical Center, Amsterdam, the Netherlands. *Dr Heufelder is in private practice in Munich, Germany.*

A total of 32 hypogonadal males with the MetS and newly diagnosed T2D (fasting plasma glucose >7.0 at baseline and/or >11.1 after a 2-hour, 75-g oral glucose tolerance test, and an elevated level of HbA_{1c}) were randomized to either supervised diet and exercise (D&E) alone or in combination with testosterone gel (50 mg once daily; Testogel; Bayer Schering

Table 1. *Patient characteristics*[a]

	D&E Plus Testosterone (n = 16)	D&E Alone (n = 16)	*P*
Age	57.3 ± 1.4	55.9 ± 1.5	.491
BMI, kg/m^2	32.1 ± 0.5	32.5 ± 0.6	.514
Waist circumference, cm	107.9 ± 1.3	105.7 ± 1.4	.260
Testosterone, nmol/L	10.5 ± 0.2	10.4 ± 0.2	.691
Free testosterone	0.2 ± 0.0	0.2 ± 0.0	.318
Bioavailable testosterone	4.5 ± 0.1	4.3 ± 0.1	.316
SHBG, nmol/L	37.9 ± 2.2	39.7 ± 2.0	.549
PSA, µg/L	2.3 ± 0.1	2.3 ± 0.1	.914
HbA_{1c}, %	7.5 ± 0.1	7.5 ± 0.1	.708
Fasting plasma glucose, mmol/L	7.9 ± 0.2	8.3 ± 0.2	.158
Insulin, pmol/L	113.2 ± 4.4	116.9 ± 6.1	.628
HDL cholesterol, mmol/L	1.05 ± 0.03	1.00 ± 0.05	.351
LDL cholesterol, mmol/L	3.8 ± 0.1	3.8 ± 0.1	.831
Triglycerides, mmol/L	3.2 ± 0.1	3.4 ± 0.3	.364
Blood pressure, mm Hg			
Systolic	140.5 ± 2.6	143.5 ± 2.1	.373
Diastolic	85.6 ± 0.9	85.0 ± 1.0	.681
HOMA-IR	5.6 ± 0.3	6.1 ± 0.4	.363
Adiponectin, µg/mL	10.1 ± 0.5	9.1 ± 0.4	.118
hsCRP, mg/dL	2.5 ± 0.1	3.0 ± 0.1	.032

Testosterone + D&E (solid bars) Vs. D&E (open bars) alone on HgA1c

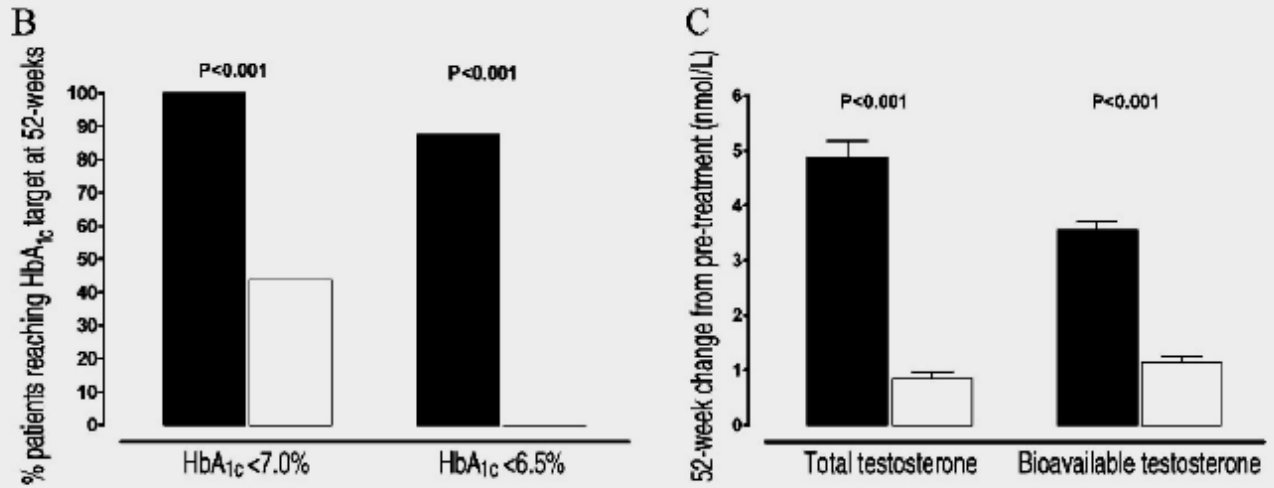
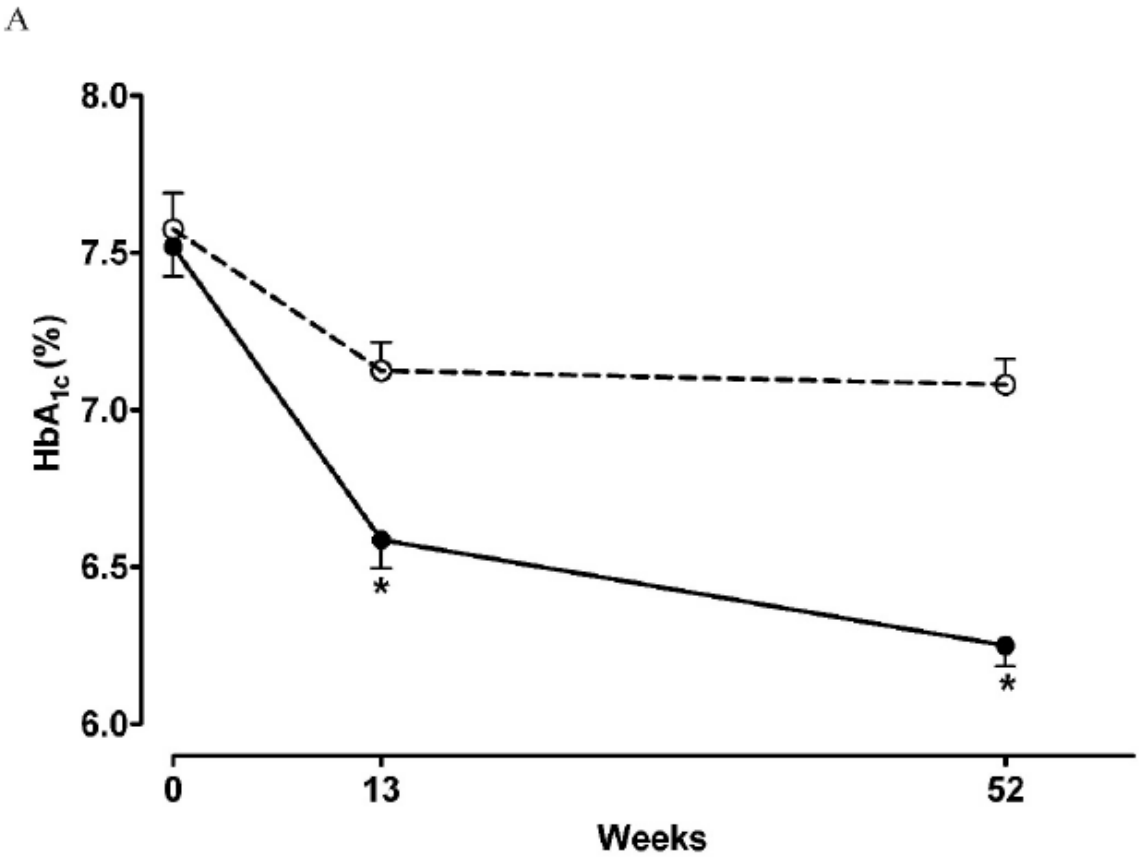


Figure 1. Glycemic control and testosterone profiles. **(A)** Glycosylated hemoglobin (HbA_{1c}) values during the course of the study. White circles indicate supervised diet and exercise alone; black circles, supervised diet and exercise in combination with transdermal testosterone administration. **(B)** Percentage of patients achieving HbA_{1c} values less than 7.0% (left) and less than 6.5% (right). White boxes indicate supervised diet and exercise alone; black boxes, supervised diet and exercise in combination with transdermal testosterone administration. **(C)** Change in serum total testosterone and bioavailable testosterone after 52-week treatment with supervised diet and exercise alone (white boxes) or in combination with transdermal testosterone administration (black boxes). Data represent mean and SE. * $P < .001$.

Testosterone + D&E (solid line) Vs. D&E (dashed line) alone on HgA1c



European Journal of Endocrinology (2006) **154** 899–906 ISSN 0804-4643

CLINICAL STUDY

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

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

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

Design: This was a double-blind placebo-controlled crossover study in 24 hypogonadal men (10 treated with insulin) over the age of 30 years with type 2 diabetes.

Methods: Patients were treated with i.m. testosterone 200 mg every 2 weeks or placebo for 3 months in random order, followed by a washout period of 1 month before the alternate treatment phase. The primary outcomes were changes in fasting insulin sensitivity (as measured by homeostatic model index (HOMA) in those not on insulin), fasting blood glucose and glycated haemoglobin. The secondary outcomes were changes in body composition, fasting lipids and blood pressure. Statistical analysis was performed on the delta values, with the treatment effect of placebo compared against the treatment effect of testosterone.

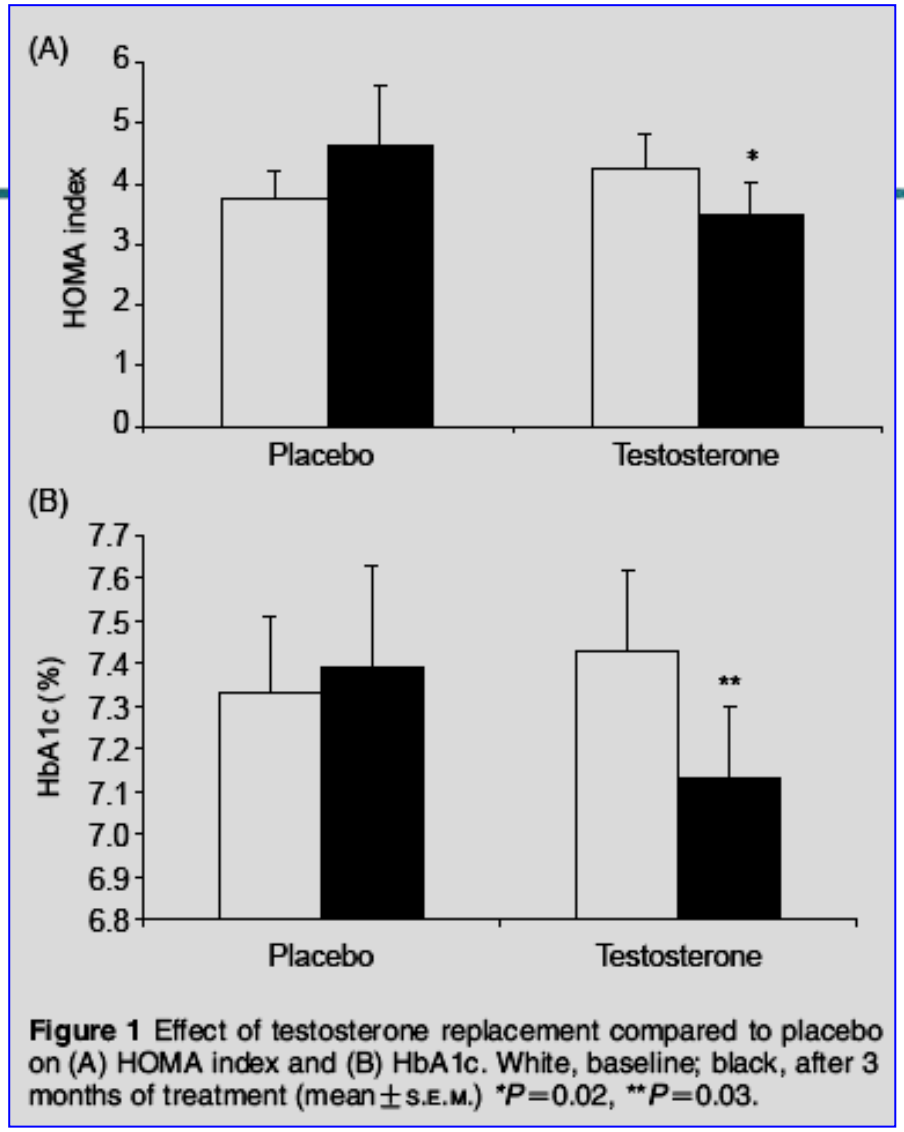


Figure 1 Effect of testosterone replacement compared to placebo on (A) HOMA index and (B) HbA1c. White, baseline; black, after 3 months of treatment (mean ± S.E.M.) *P=0.02, **P=0.03.

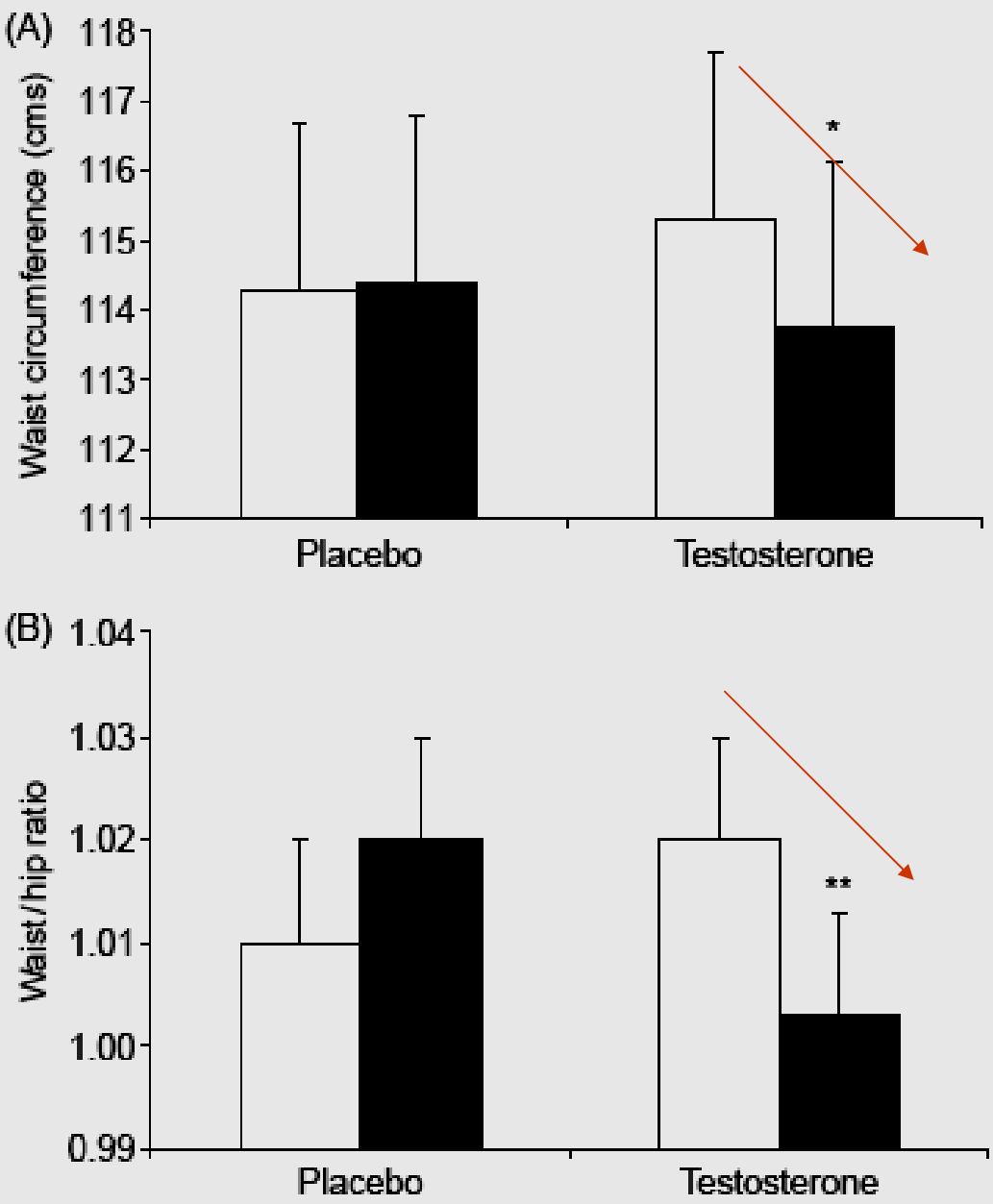


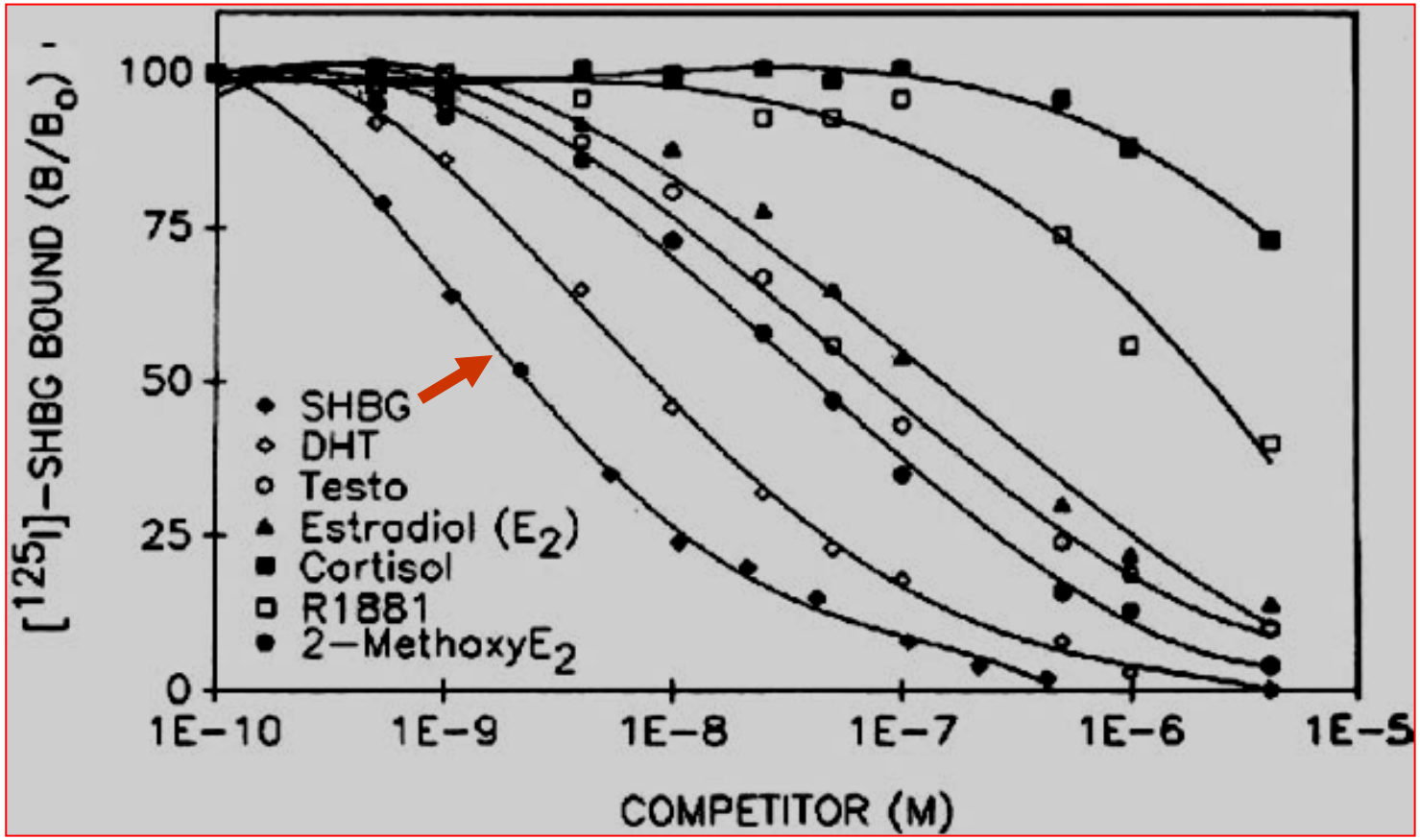
Figure 2 Effect of testosterone replacement compared to placebo on (A) waist circumference and (B) waist/hip ratio (mean ± S.E.M.) *$P = 0.03$, **$P = 0.01$ vs placebo.

SHBG Receptor and associated signaling

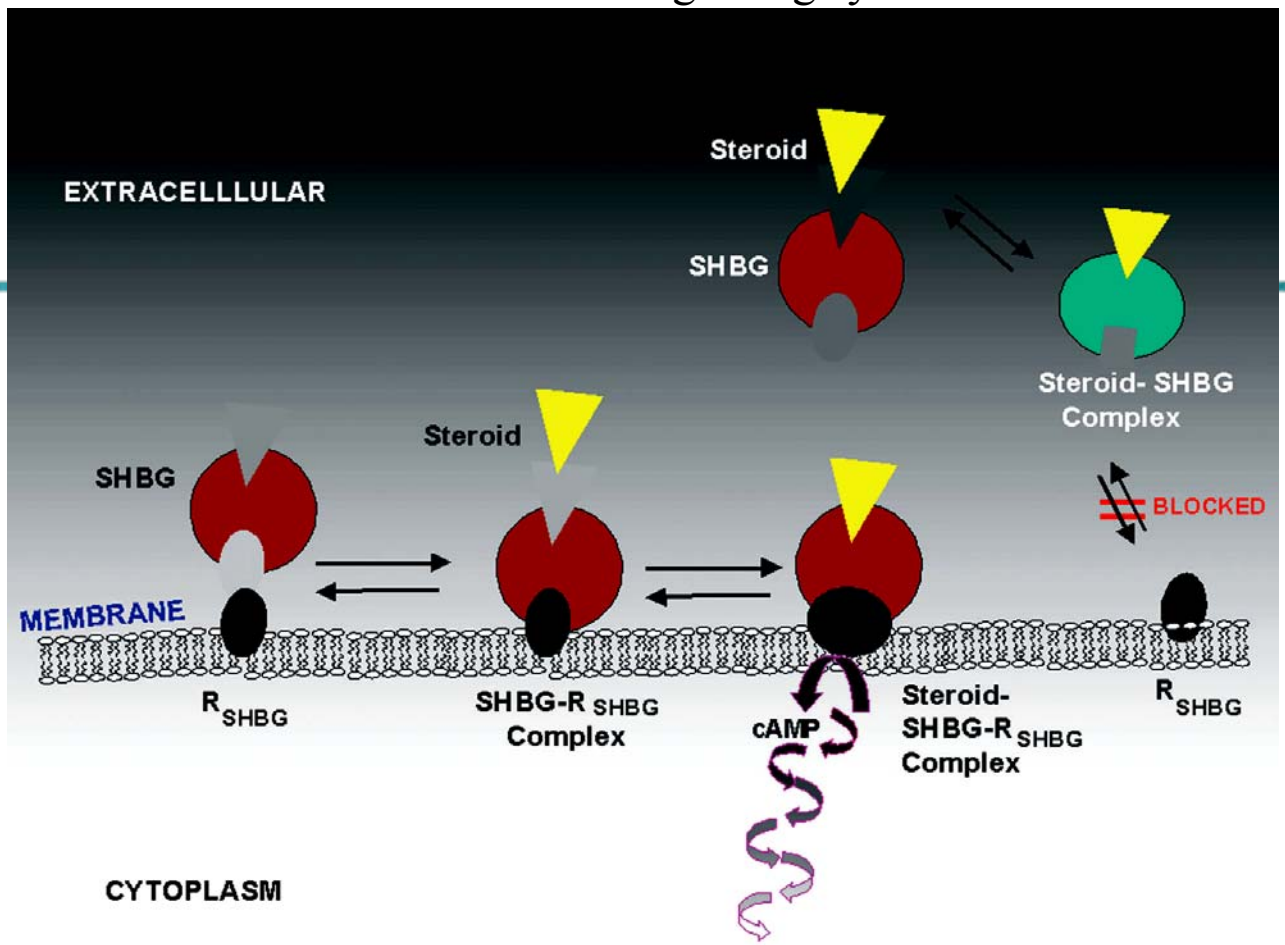
Specific, high-affinity binding sites detected for SHBG on

- Uterine endometrial cell membranes (Strel'chyonok *et al.* 1984)
- Prostatic cell membranes (Hryb *et al.* 1985)
- Human placenta (Avvakumov *et al.* 1985).
- MCF-7 breast cancer cells (Frairia *et al.* 1991, Porto *et al.* 1992*b*, Fissore *et al.* 1994),
- Normal breast (Frairia *et al.* 1991),
- Liver (Frairia *et al.* 1991, Fortunati *et al.* 1992*a*)
- Epididymis (Guéant *et al.* 1991, Felden *et al.* 1992, Porto *et al.* 1992*a*, Krupenko *et al.*1994),

Inhibition of the binding of 125I-SHBG to the soluble RSHBG by steroids (from Hryb *et al.* 1990).



The SHBG signaling system



In its steroid-free configuration, SHBG binds to RSHBG on cell membranes, forming a bipartite complex (SHBG–RSHBG). SHBG, already bound to a steroid, non-competitively inhibits the binding of SHBG to RSHBG. However, within minutes after exposure of SHBG–RSHBG to a steroid agonist, e.g. estradiol (Nakhla *et al.* 1990, 1994) or 5-androstan,3,17-diol (Nakhla *et al.* 1995), a tripartite complex (steroid–SHBG–RSHBG) forms that activate adenylate cyclase, leading to the generation of the second messenger, cAMP.

Kahn et al, J Endocrinol 2002

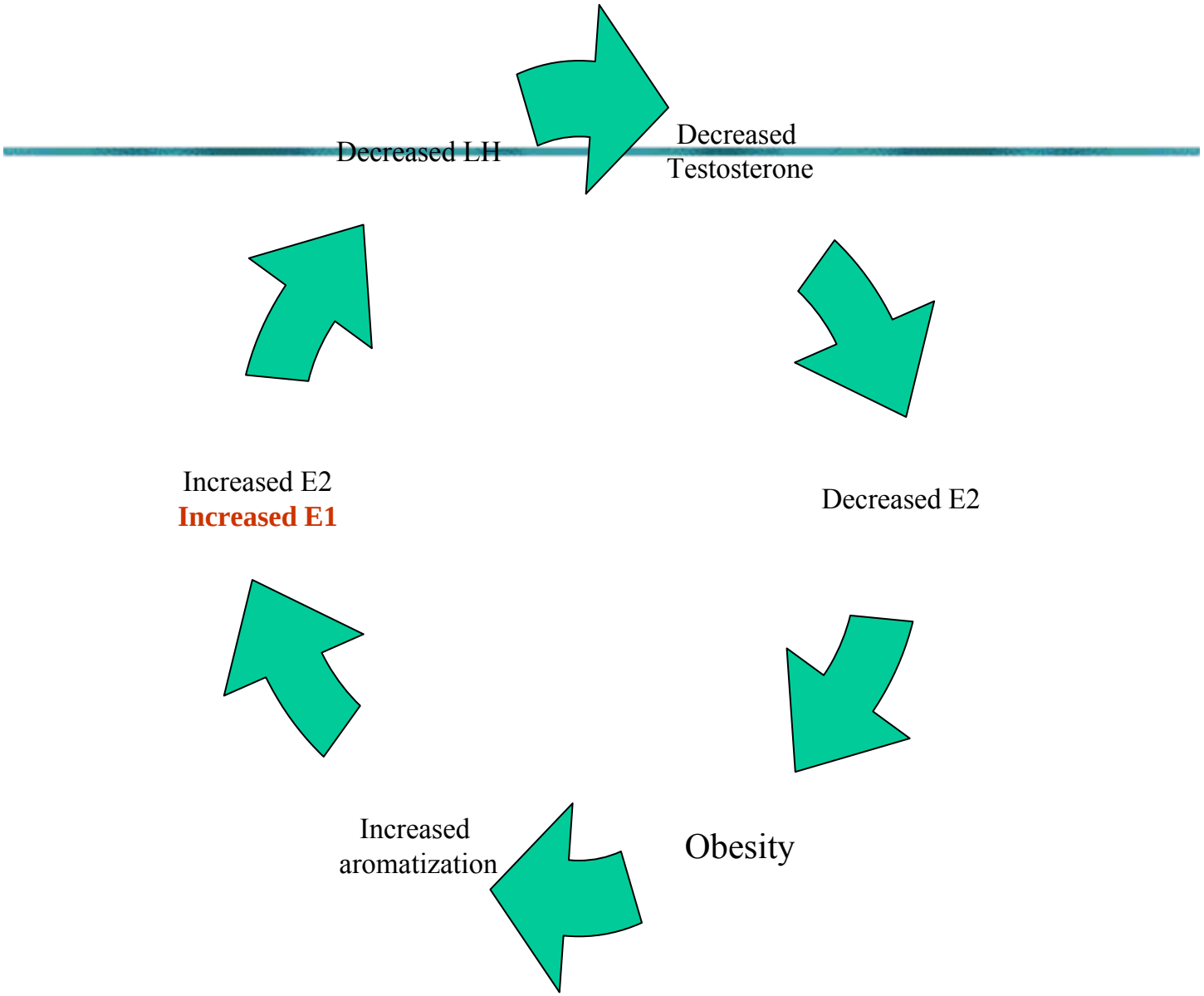
SHBG-receptor dependent biologic functions

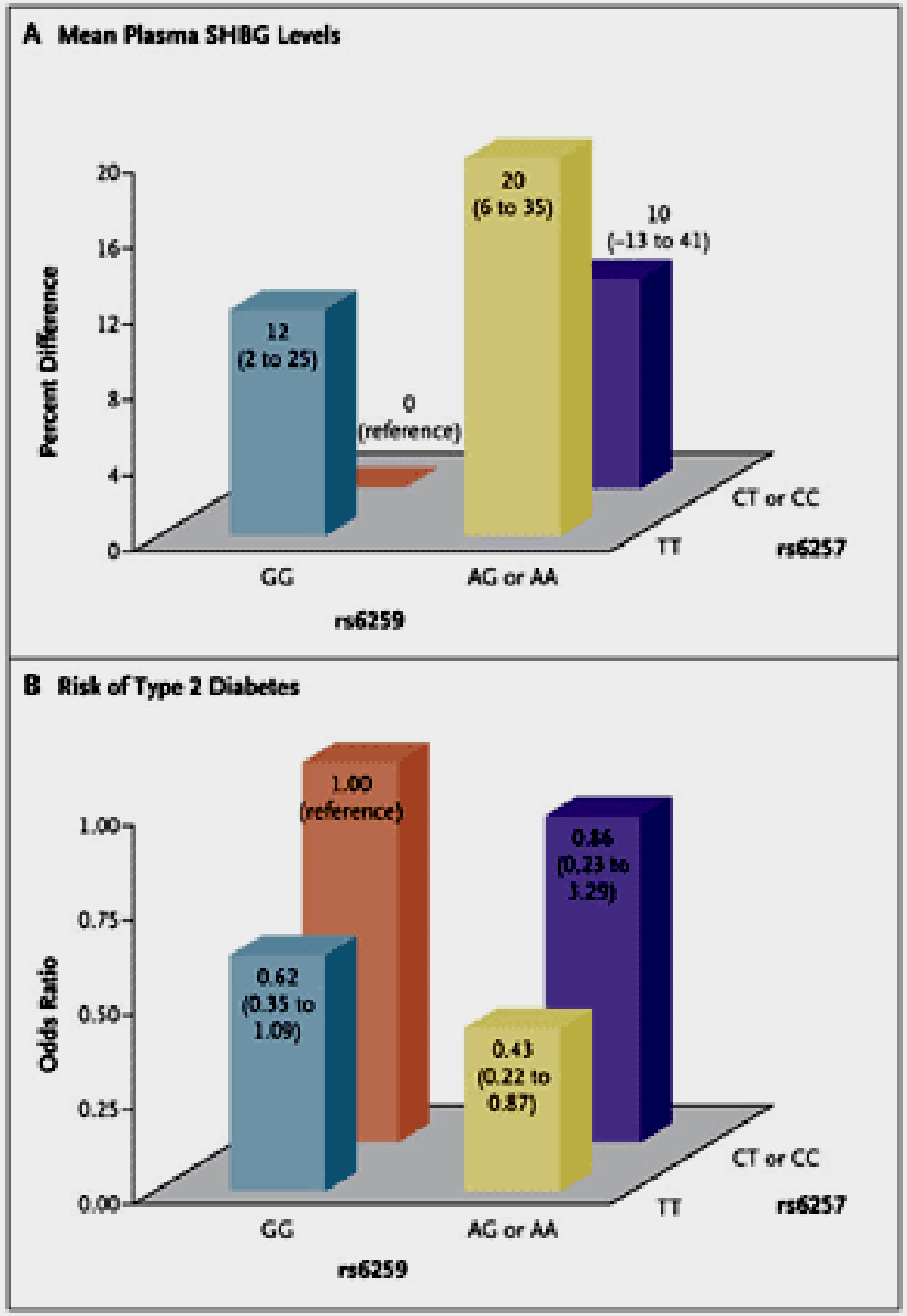
- PSA: Prostate explants secrete PSA when treated with DHT; however, they do not when treated with estradiol, which does not bind to the AR. When such explants were treated first with SHBG, and then with estradiol, they produced PSA at concentrations similar to those seen when they were exposed to DHT.
- Decreases the estrogen-mediated growth of the human breast carcinoma cell line, MCF-7

Testosterone in the Metabolic Syndrome

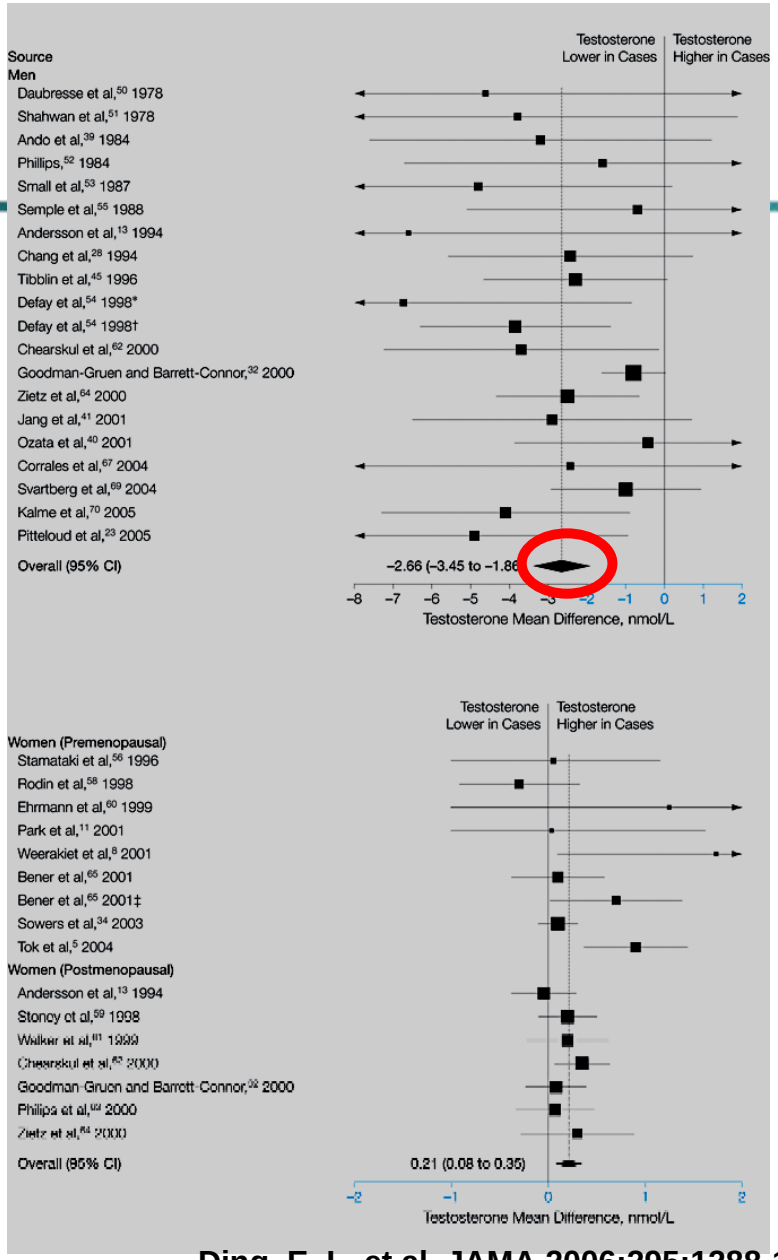
- Measuring testosterone is relevant
- Actual measurement works better than looking up formulas on the internet (***but is clearly much less fun).***
- Hypoandrogenism is likely causally linked to the metabolic syndrome but ling term data is not available

- עד כאן


Decreased LH
Decreased Testosterone
Decreased E2
Obesity
Increased aromatization
Increased E2
Increased E1


A Mean Plasma SHBG Levels
Percent Difference
20
16
12
8
4
0
12
(2 to 25)
0
(reference)
20
(6 to 35)
10
(−13 to 41)
GG
AG or AA
rs6259
CT or CC
TT
rs6257
B Risk of Type 2 Diabetes
Odds Ratio
1.00
0.75
0.50
0.25
0.00
1.00
(reference)
0.62
(0.35 to
1.09)
0.43
(0.22 to
0.87)
0.86
(0.23 to
3.29)
GG
AG or AA
rs6259
CT or CC
TT
rs6257

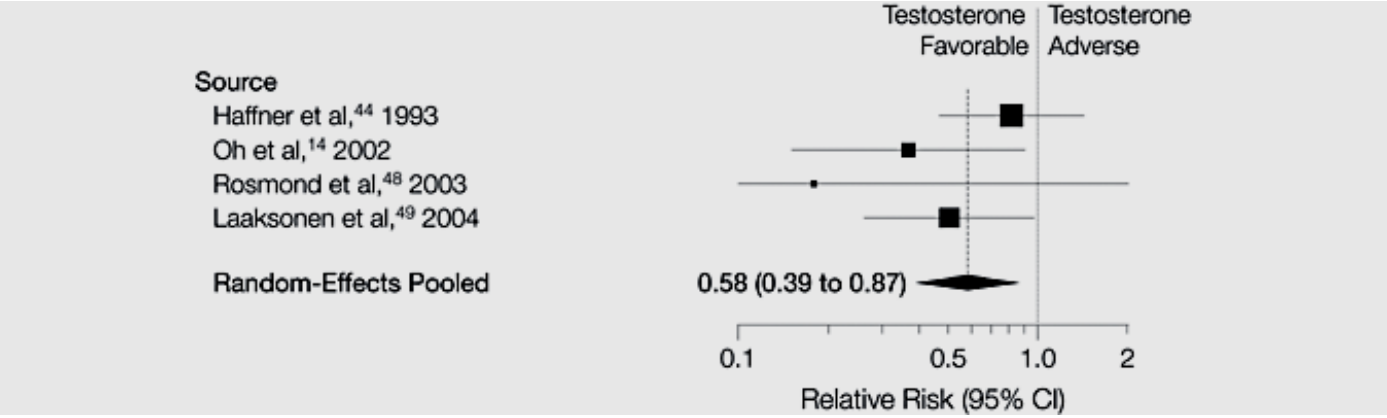
Random-Effects Pooled Mean Difference of Testosterone Levels Between Type 2 Diabetes Cases and Controls, Men and Women



JAMA

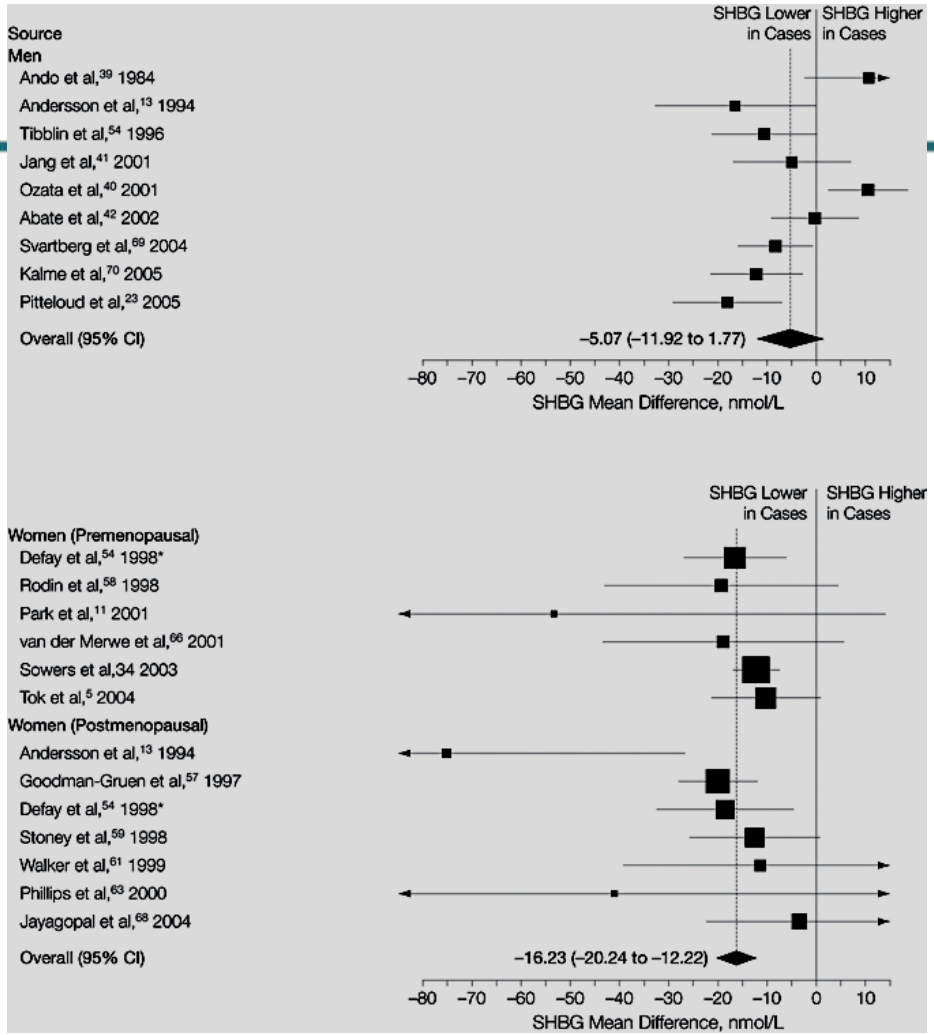
Ding, E. L. et al. JAMA 2006;295:1288-1299.

Random-Effects Pooled Relative Risks of Testosterone and Type 2 Diabetes from Prospective Studies in Men



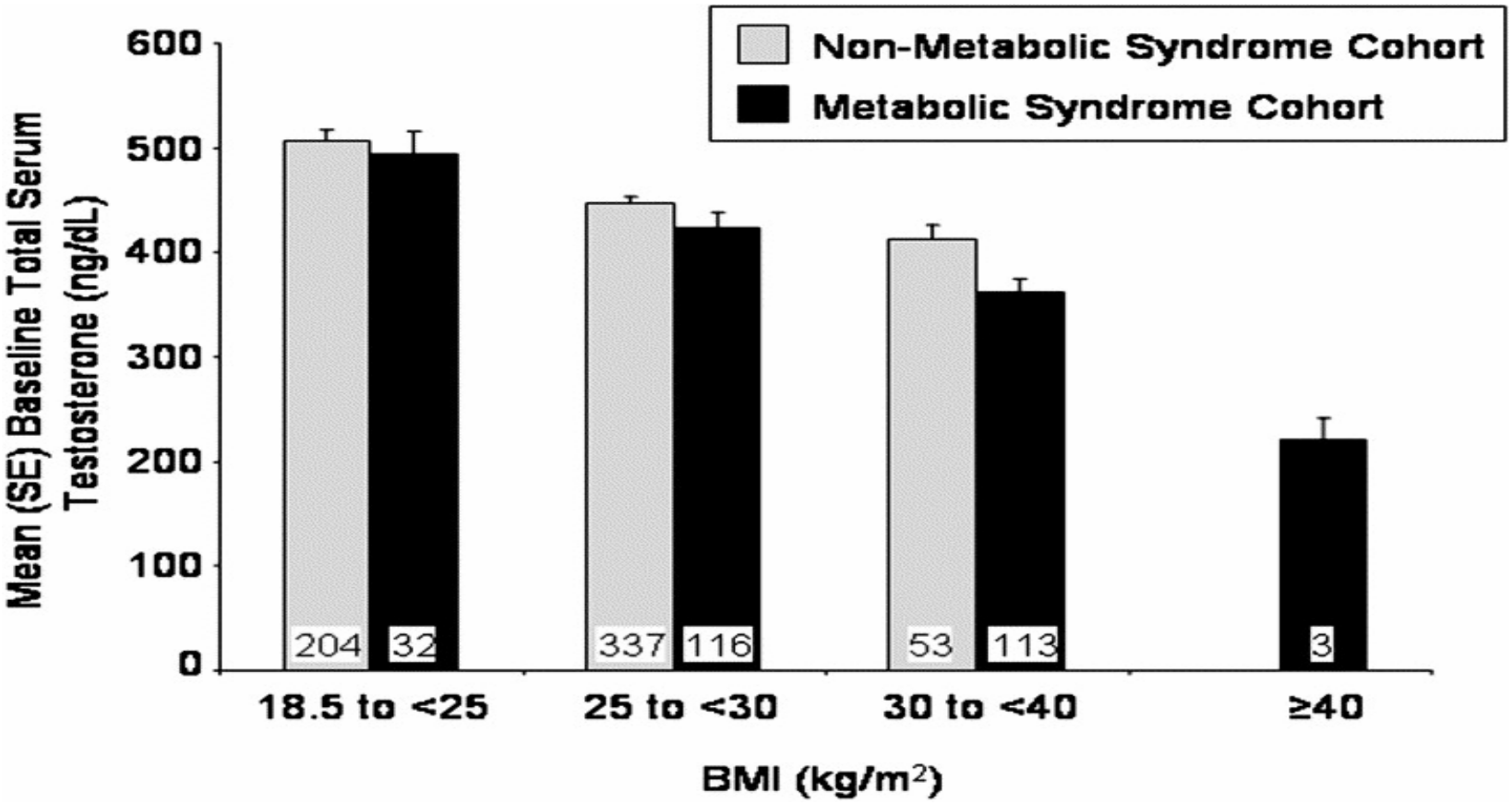
Ding, E. L. et al. JAMA 2006;295:1288-1299.

Random-Effects Pooled Mean Difference of Sex Hormone-Binding Globulin Levels Between Type 2 Diabetes Cases and Controls, Men and Women

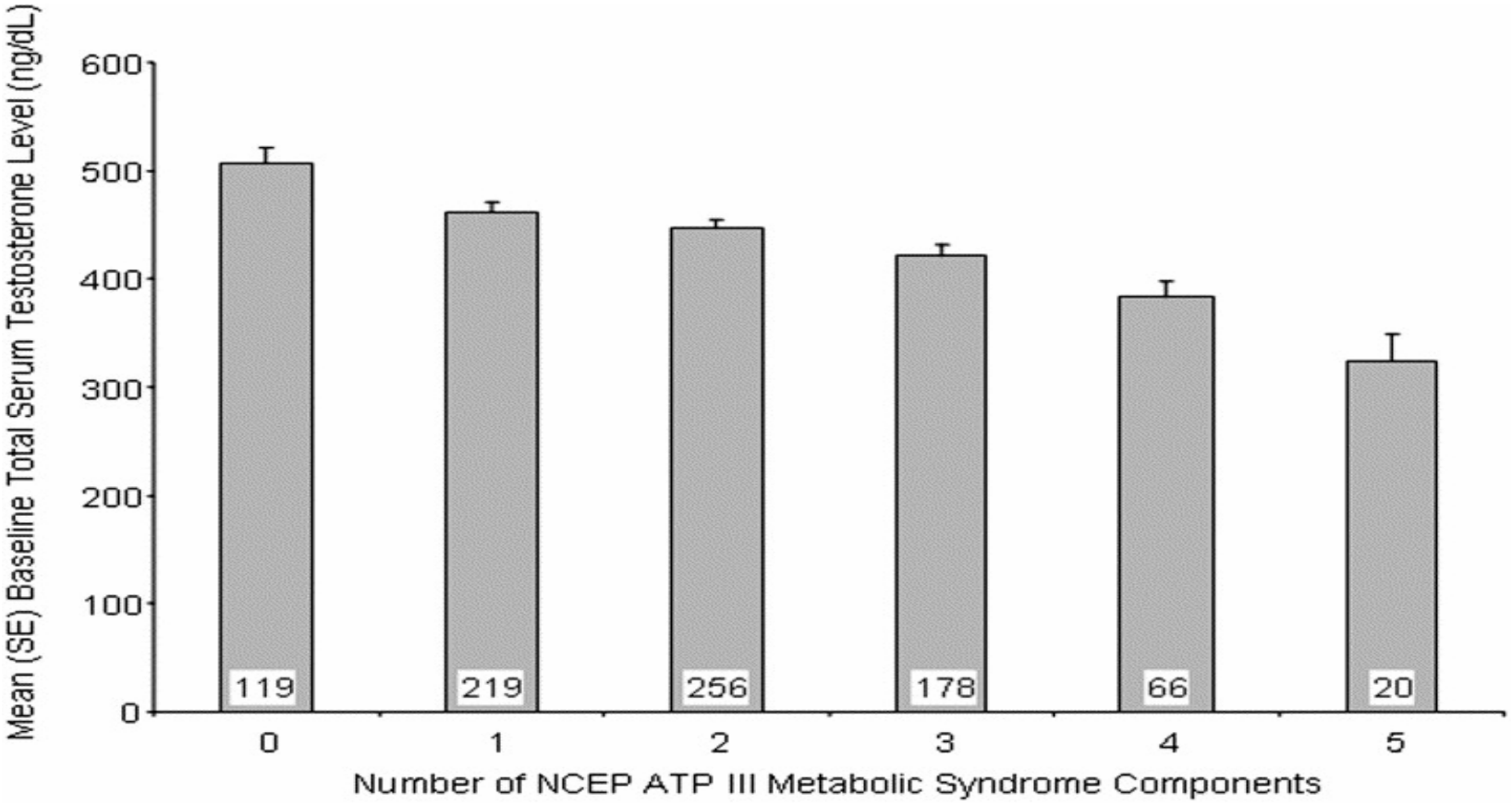


Ding, E. L. et al. JAMA 2006;295:1288-1299.

Relationship among total serum testosterone, BMI and metabolic syndrome .

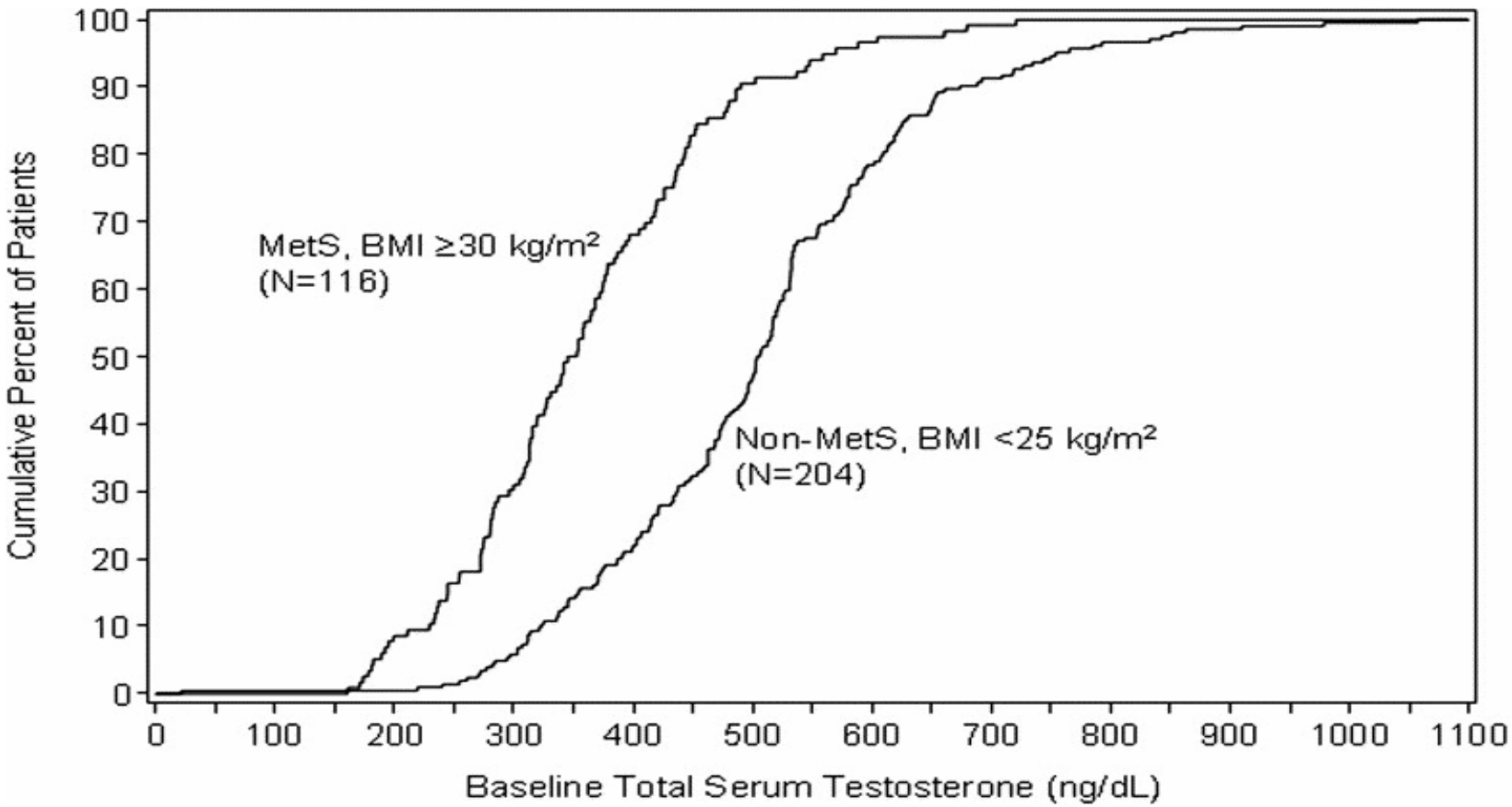


Mean baseline total serum testosterone levels among patients with none, 1, 2, 3, 4 or all 5 of NCEP ATP III metabolic syndrome components .



Kaplan et al, J urol 176:1524, 2006

Cumulative percent population baseline total serum testosterone distribution curves for lean men (BMI less than 25 kg/m (2without MetS vs obese men (BMI 30 kg/m 2or greater) with MetS .

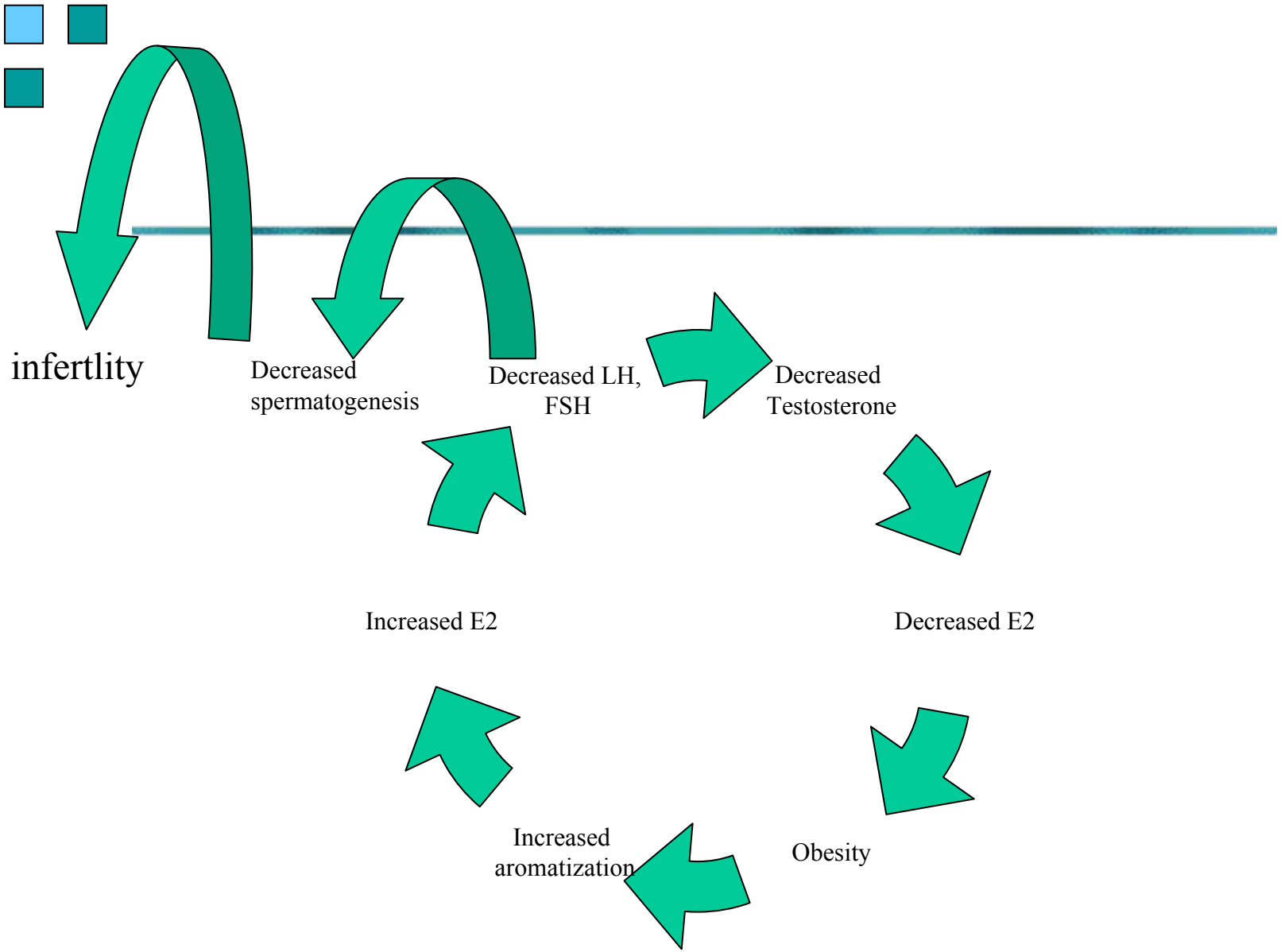


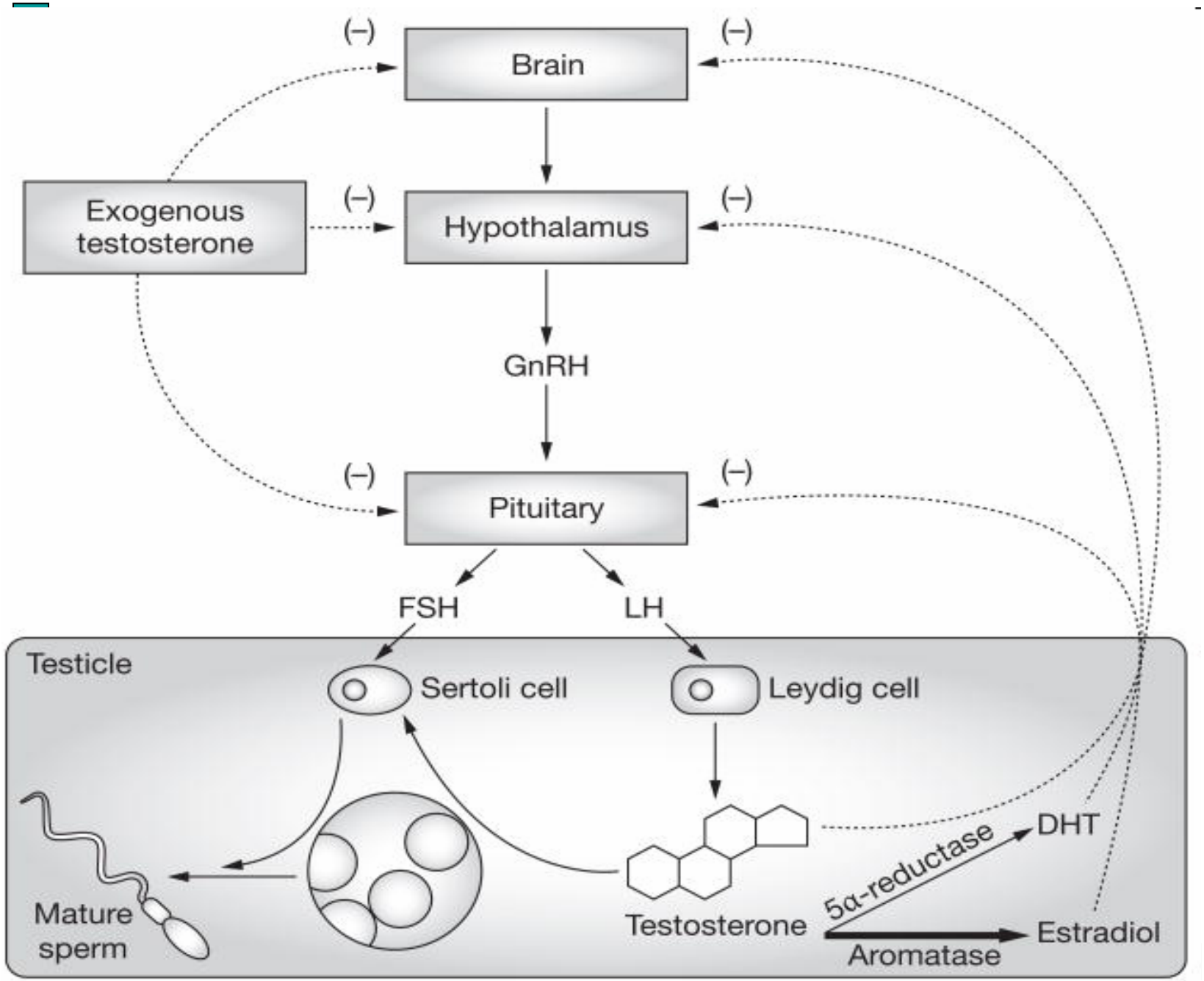
Kaplan et al, J urol 176:1524, 2006

The Age Related Decrease in Testosterone is Significantly Exacerbated in Obese Men With the Metabolic Syndrome

- Baseline total serum testosterone, lipid, glycemic and anthropometric data were obtained from 864 men (mean age 52 years) participating in 2 lipid treatment studies.
- Inclusion criteria for the 2 studies included low-density lipoprotein cholesterol 130 to 160 mg/dl and triglycerides 350 mg/dl or less.
- Mean baseline total serum testosterone levels in obese and severely obese aging men with the metabolic syndrome were around 150 and 300 ng/dl, respectively, less than that in aging, lean men with no metabolic syndrome.

Kaplan et al, J urol 176:1524, 2006


infertlity
Decreased spermatogenesis
Decreased LH, FSH
Decreased Testosterone
Decreased E2
Obesity
Increased aromatization
Increased E2


(–)
Brain
(–)
Exogenous testosterone
(–)
Hypothalamus
(–)
GnRH
(–)
Pituitary
(–)
FSH
LH
Testicle
Sertoli cell
Leydig cell
Mature sperm
Testosterone
5α-reductase
DHT
Aromatase
Estradiol

Hypogonadotropic Hypogonadism of Obesity

- A 29-year-old man presented to a clinic with infertility and hypogonadism in the setting of morbid obesity.
- On presentation, he had notable gynecomastia and a low testicular volume.
- The patient's weight was 154 kg and his height was 168 cm (BMI 54.5 kg/m2). Before referral to the clinic, the patient had been treated with testosterone therapy for 4 months for hypogonadism. This treatment had caused his initially low sperm concentration to fall to undetectable levels.
- Investigations—Measurement of reproductive hormone levels, pituitary MRI, and semen analysis.

Nat Clin Pract Endocrinol Metab. 2008; 4: 415–419.

Hypogonadotropic Hypogonadism of Obesity

- low total testosterone levels (5.25 nmol/l [151.2 ng/dl]; normal range 7.7–27.3 nmol/l [221.8–786.2 ng/dl])
- low levels of calculated free testosterone (102.2 pmol/l [2.9 pg/ml]; normal range 105–490 pmol/l [3.0–14.1 pg/ml])
- normal levels of sex hormone-binding globulin (34.8 nmol/l; normal range 13.0–71.0 nmol/l).
- Luteinizing hormone (LH) <1 IU/l (normal range 1–14 IU/l)
- FSH- 2 IU/l (normal range 1–14 IU/l).
- Serum estradiol within the normal range (73–275 pmol/l [20–75 pg/ml]) with a level of 172 pmol/l (47 pg/ml).

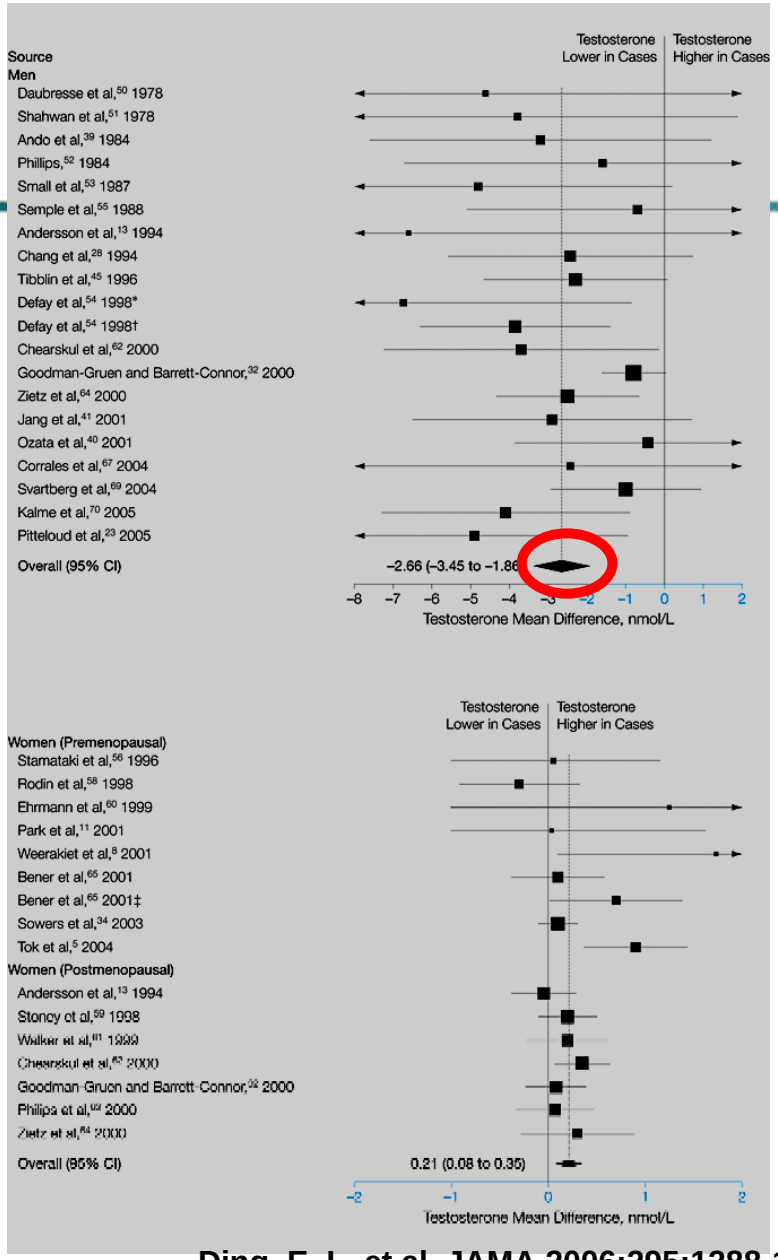
Roth MY et al, Nat Clin Pract Endocrinol Metab. 2008; 4: 415–419.

- In obese men, increased adipose tissue results in increased aromatase activity and a relative elevation in estradiol levels, which inhibits gonadotropin secretion from the pituitary.

- Men with an increased BMI have a linear rise in serum 17β-estradiol. However, estradiol levels in obese men do not frequently surpass the normal range
- The ratio of testosterone to estradiol is more clinically useful in diagnosing estrogen excess in men than the absolute estradiol level alone

- Assessment of estradiol levels in men can be particularly challenging since most clinical assays are optimized to measure levels in the normal female range and are not well validated for measurement of male estradiol levels.
- Clearly, clinical symptoms such as gynecomastia as well as laboratory data should be considered in the evaluation of hypogonadotropic hypogonadism.

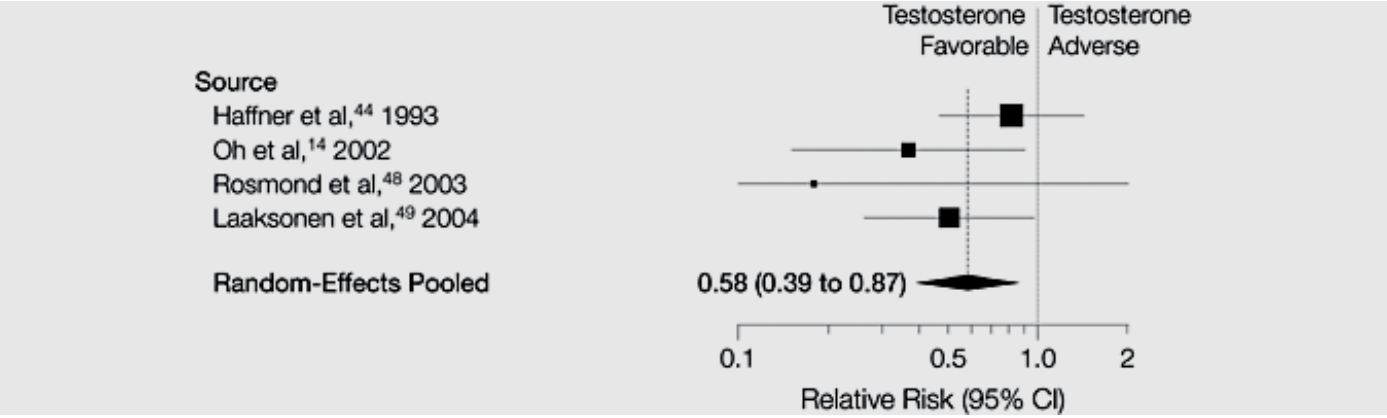
Random-Effects Pooled Mean Difference of Testosterone Levels Between Type 2 Diabetes Cases and Controls, Men and Women



JAMA

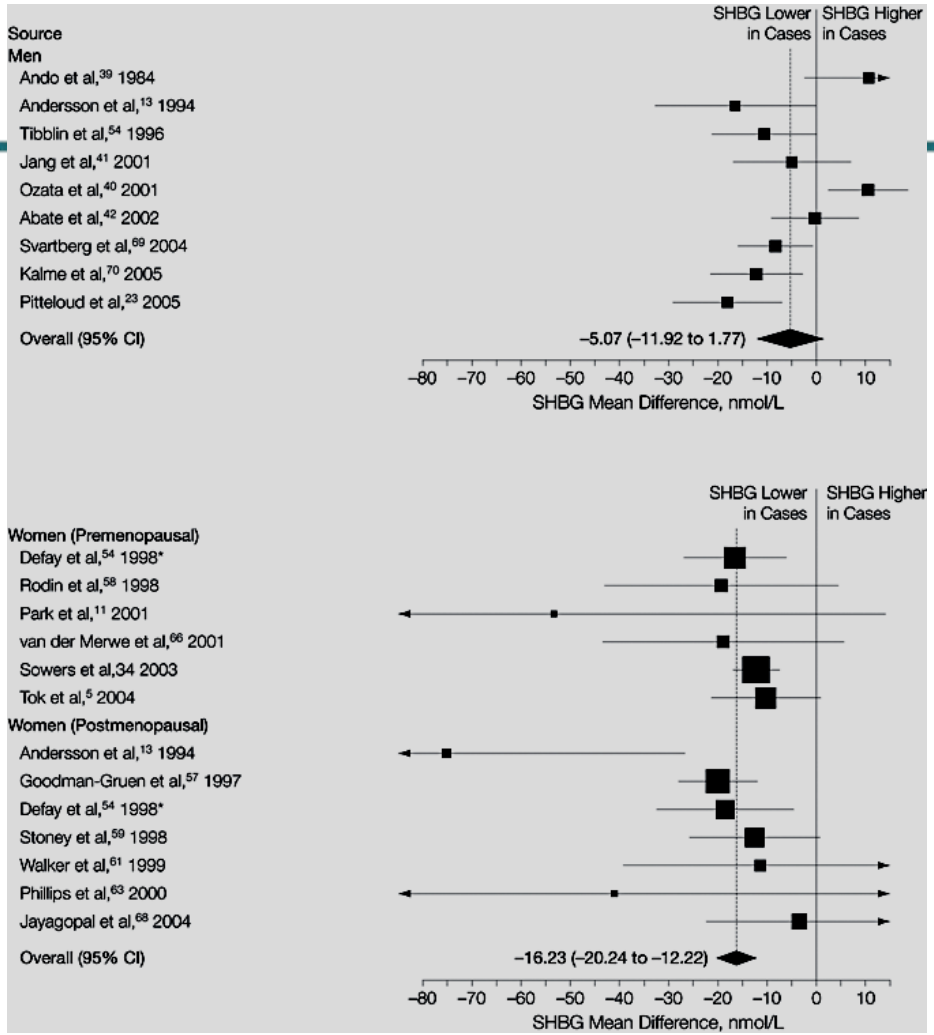
Ding, E. L. et al. JAMA 2006;295:1288-1299.

Random-Effects Pooled Relative Risks of Testosterone and Type 2 Diabetes from Prospective Studies in Men



Ding, E. L. et al. JAMA 2006;295:1288-1299.

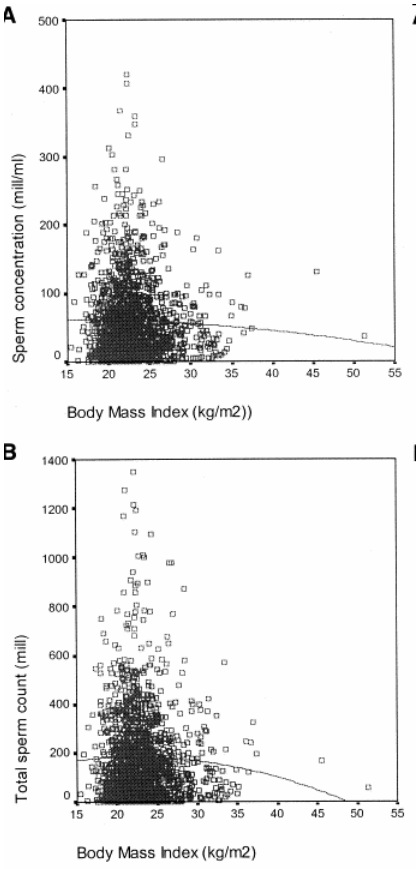
Random-Effects Pooled Mean Difference of Sex Hormone-Binding Globulin Levels Between Type 2 Diabetes Cases and Controls, Men and Women



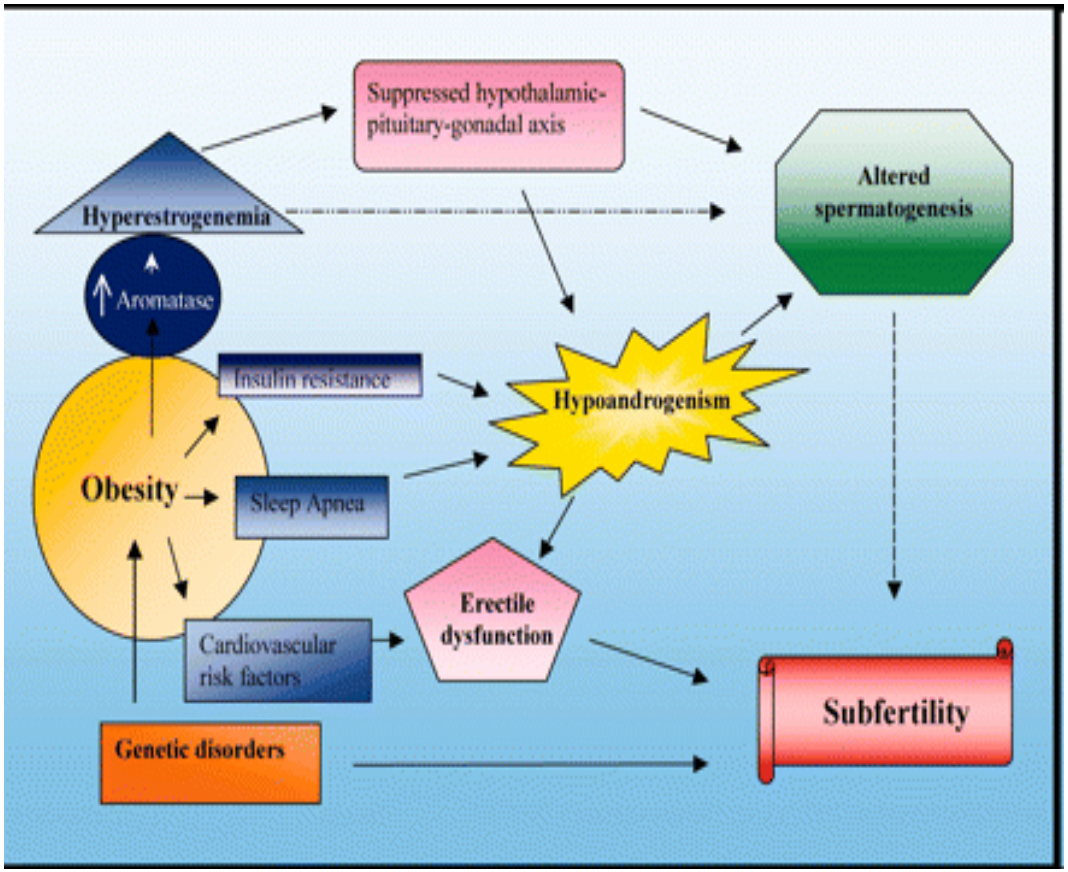
Ding, E. L. et al. JAMA 2006;295:1288-1299.

Testosterone, estradiol, SHBG and the risk of type 2 DM in men

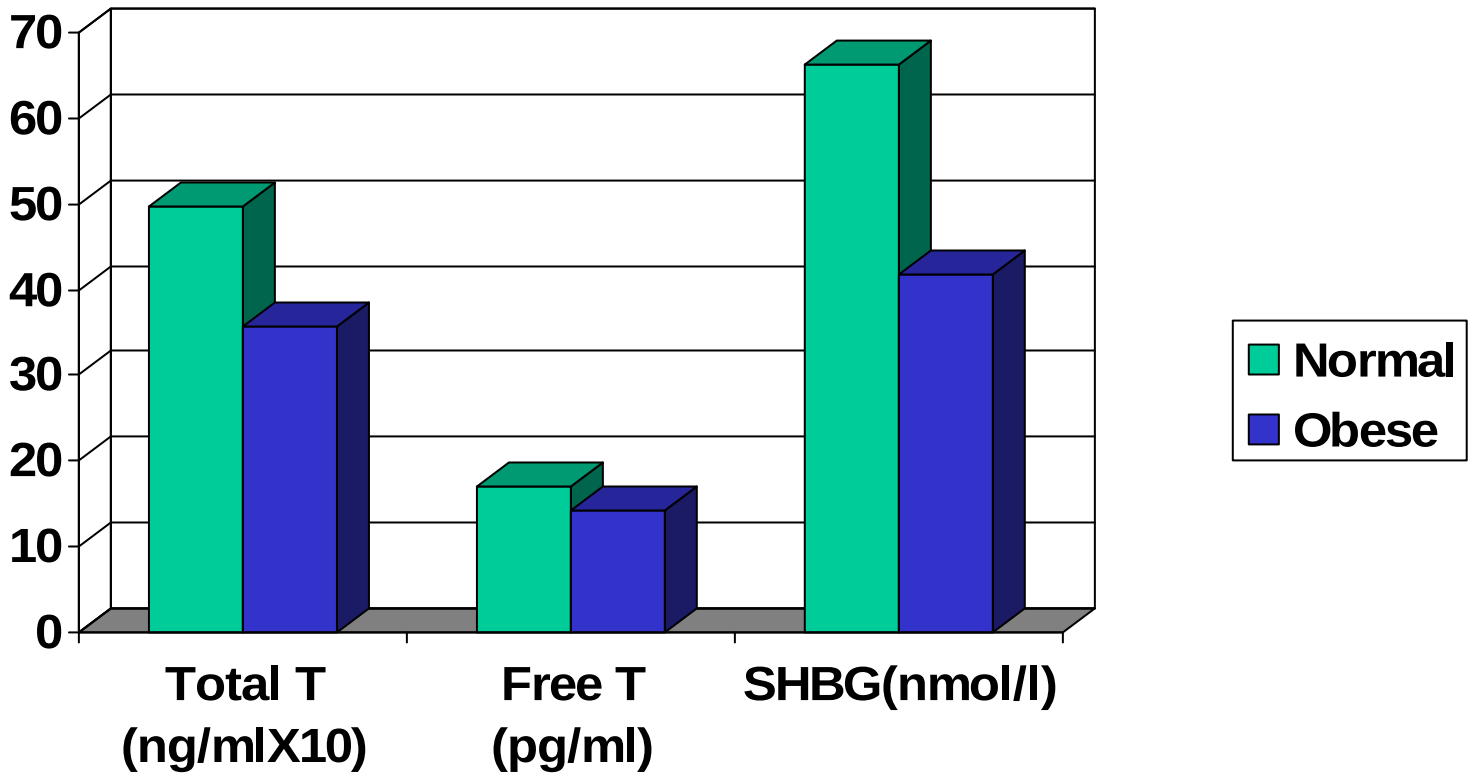
- Low testosterone levels were associated with higher risk of type 2 diabetes among men
- Low plasma levels of SHBG were weakly associated with type 2 diabetes in men
- Endogenous estradiol levels may be elevated both in men and in postmenopausal women with type 2 diabetes.


A
Sperm concentration (mill/ml)
500
400
300
200
100
0
15
20
25
30
35
40
45
50
55
Body Mass Index (kg/m2))
B
Total sperm count (mill)
1400
1200
1000
800
600
400
200
0
15
20
25
30
35
40
45
50
55
Body Mass Index (kg/m2)

Potential mechanisms for hypoandrogenism and erectile dysfunction in obese males .



Androgens in obese men

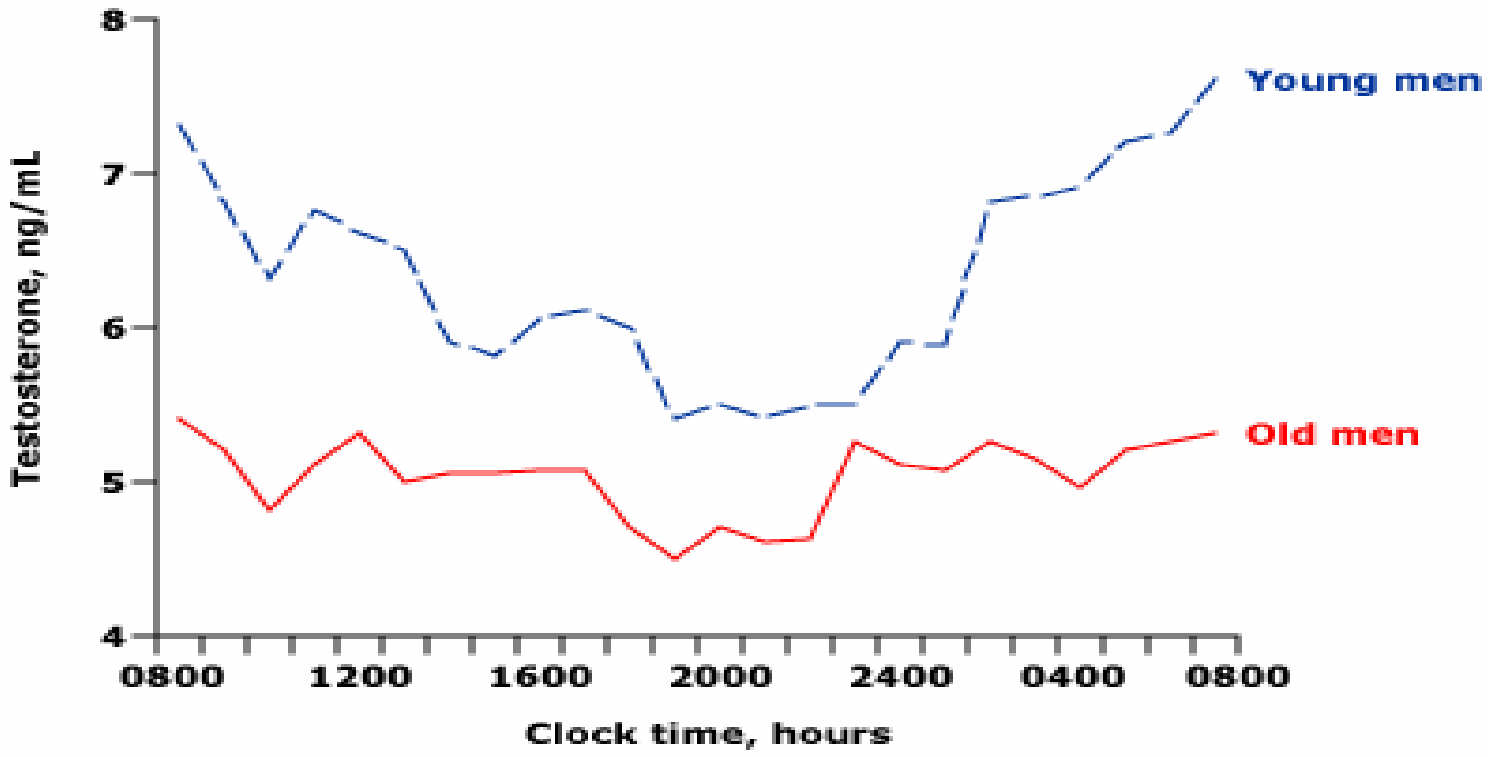


Pasquali et al, Metabolism. 1991; ;40:101-4

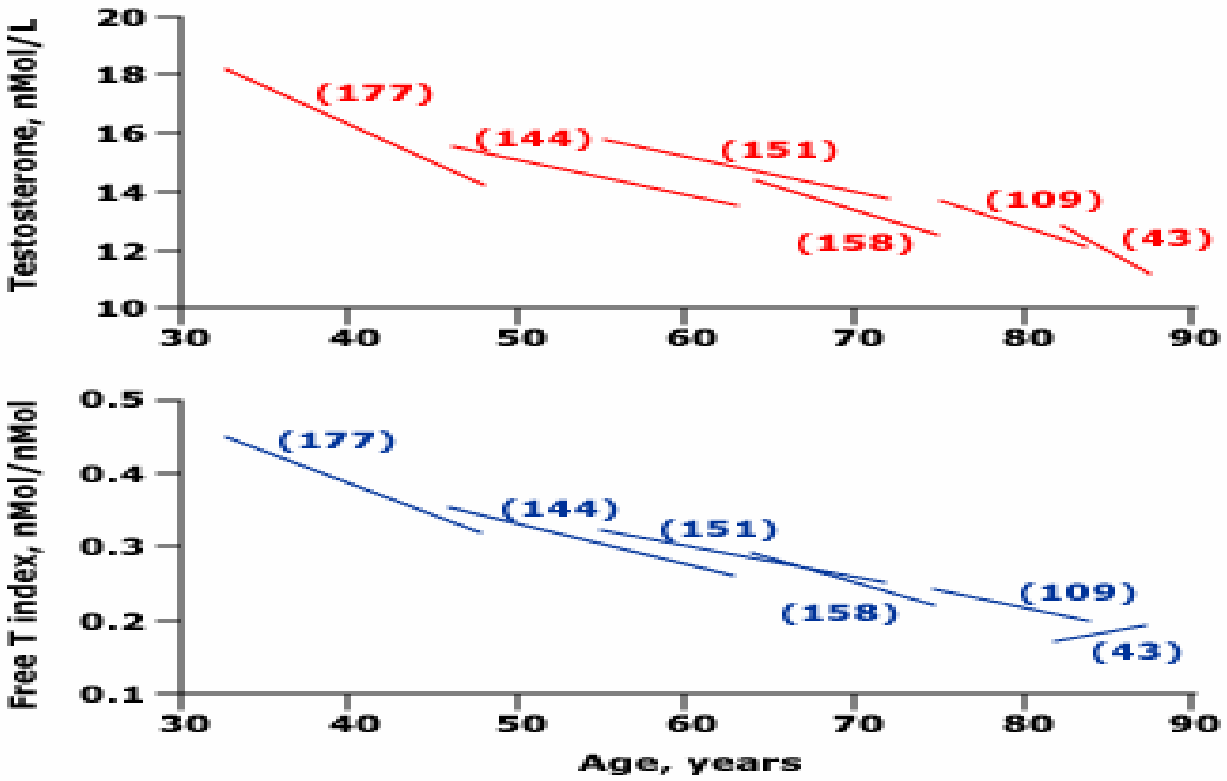
Indication for testosterone replacement in men>50y

- [1] clinical manifestations indicative of ADAM (osteopenia, decreased muscle mass and strength, decline in stamina and energy, low libido, loss of erectile quality, irritability, impaired cognition, or other mood changes);
- [2] a low serum testosterone, bioavailable testosterone, or FTI; *and*
- [3] no contraindications to treatment.

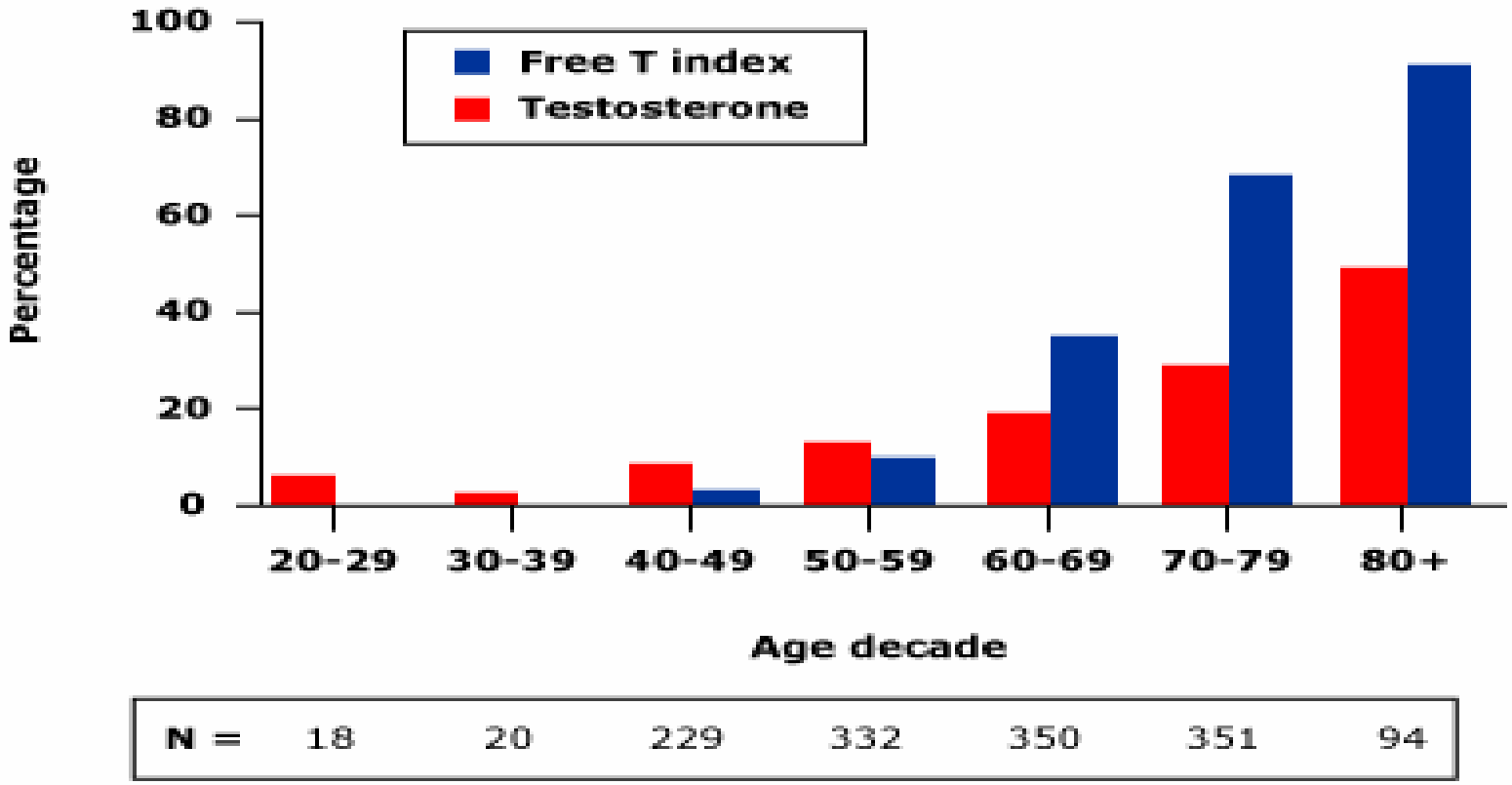
Variation in serum total testosterone concentrations



Longitudinal effects of aging



J Clin Endocrinol Metab 2001; 86:724



Percent of men in each 10-yr interval, from the third to the ninth decades, with at least one total testosterone <325 ng/dL (11.3 nmol/L) (red bars), or T/SHBG (free T index) <0.153 nmol/nmol (blue bars). : Harman, SM, Metter, EJ, Tobin, JD, Pearson, J. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging.

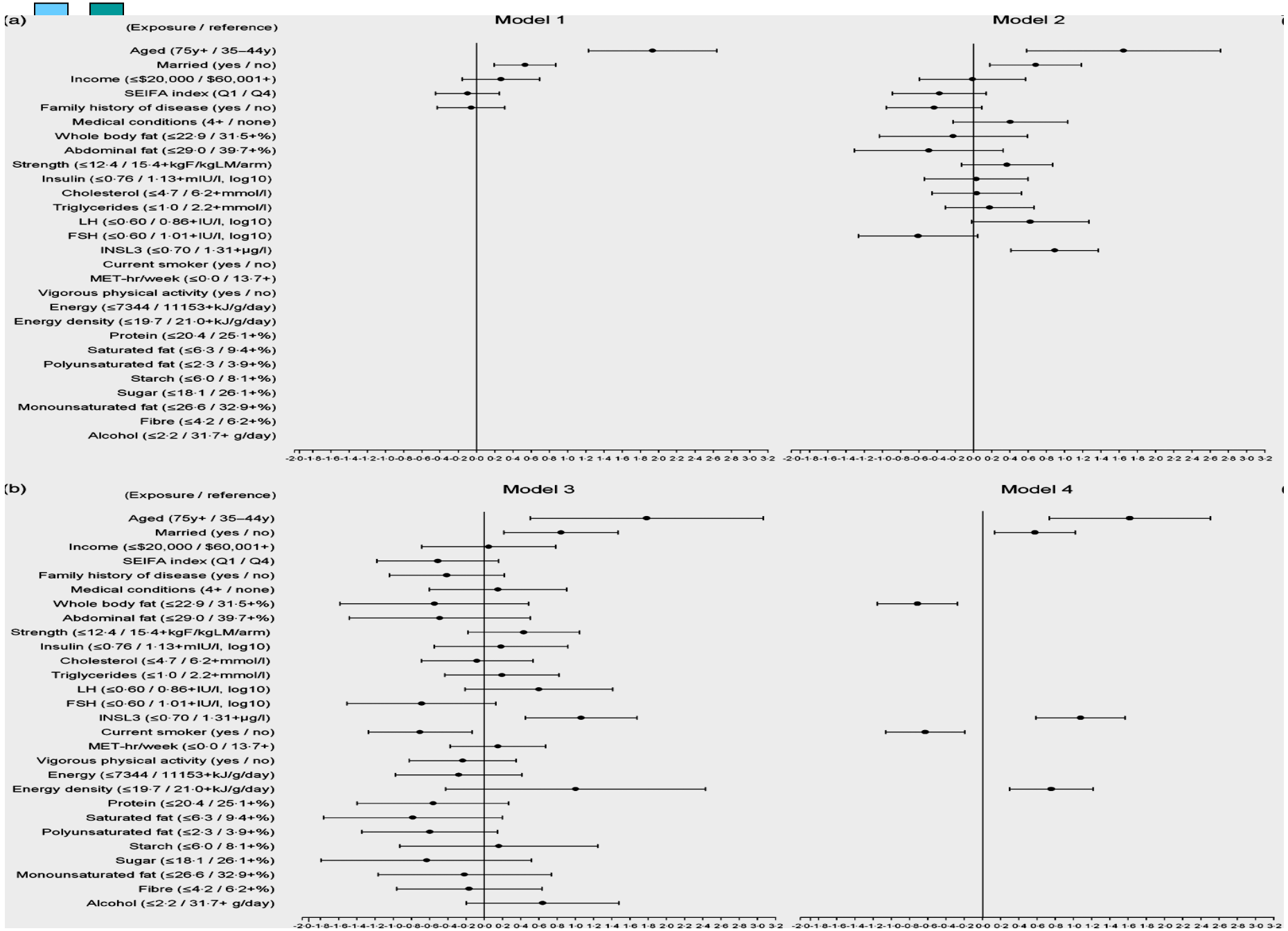
J Clin Endocrinol Metab 2001; 86:724.

Liverman, CT, Blazer, DG, eds. Testosterone and aging: clinical research directions. Washington, D.C.: National Academies Press 2004 .

The Endocrine Society's evidence-based clinical guidelines for testosterone therapy in adult men with androgen deficiency- 2006.

In the absence of known pituitary or testicular disease, we suggest testosterone therapy only for men with unequivocally and reproducibly low serum testosterone concentrations (<200 ng/dL, 6.9 nmol/L) and clinically important symptoms of androgen deficiency. Physicians must discuss the uncertainty about the risks and benefits of testosterone therapy before recommending this approach.

The target serum testosterone concentration in these men should be lower than that for younger men, for example, 300 to 400 ng/dL, rather than 500 to 600 ng/dL, to minimize the potential risk of testosterone-dependent diseases.


(a)
(Exposure / reference)
Model 1
Model 2
Aged (75y+ / 35–44y)
Married (yes / no)
Income (≤$20,000 / $60,001+)
SEIFA index (Q1 / Q4)
Family history of disease (yes / no)
Medical conditions (4+ / none)
Whole body fat (≤22·9 / 31·5+%)
Abdominal fat (≤29·0 / 39·7+%)
Strength (≤12·4 / 15·4+kgF/kgLM/arm)
Insulin (≤0·76 / 1·13+mIU/l, log10)
Cholesterol (≤4·7 / 6·2+mmol/l)
Triglycerides (≤1·0 / 2.2+mmol/l)
LH (≤0·60 / 0·86+IU/l, log10)
FSH (≤0·60 / 1·01+IU/l, log10)
INSL3 (≤0·70 / 1·31+µg/l)
Current smoker (yes / no)
MET-hr/week (≤0·0 / 13·7+)
Vigorous physical activity (yes / no)
Energy (≤7344 / 11153+kJ/g/day)
Energy density (≤19·7 / 21·0+kJ/g/day)
Protein (≤20·4 / 25·1+%)
Saturated fat (≤6·3 / 9·4+%)
Polyunsaturated fat (≤2·3 / 3·9+%)
Starch (≤6·0 / 8·1+%)
Sugar (≤18·1 / 26·1+%)
Monounsaturated fat (≤26·6 / 32·9+%)
Fibre (≤4·2 / 6·2+%)
Alcohol (≤2·2 / 31·7+ g/day)
-2·0 -1·8 -1·6 -1·4 -1·2 -1·0 -0·8 -0·6 -0·4 -0·2 0·0 0·2 0·4 0·6 0·8 1·0 1·2 1·4 1·6 1·8 2·0 2·2 2·4 2·6 2·8 3·0 3·2
(b)
(Exposure / reference)
Model 3
Model 4
Aged (75y+ / 35–44y)
Married (yes / no)
Income (≤$20,000 / $60,001+)
SEIFA index (Q1 / Q4)
Family history of disease (yes / no)
Medical conditions (4+ / none)
Whole body fat (≤22·9 / 31·5+%)
Abdominal fat (≤29·0 / 39·7+%)
Strength (≤12·4 / 15·4+kgF/kgLM/arm)
Insulin (≤0·76 / 1·13+mIU/l, log10)
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LH (≤0·60 / 0·86+IU/l, log10)
FSH (≤0·60 / 1·01+IU/l, log10)
INSL3 (≤0·70 / 1·31+µg/l)
Current smoker (yes / no)
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Fibre (≤4·2 / 6·2+%)
Alcohol (≤2·2 / 31·7+ g/day)
-2·0 -1·8 -1·6 -1·4 -1·2 -1·0 -0·8 -0·6 -0·4 -0·2 0·0 0·2 0·4 0·6 0·8 1·0 1·2 1·4 1·6 1·8 2·0 2·2 2·4 2·6 2·8 3·0 3·2

The Florey Adelaide Male Ageing Study (FAMAS)

- A regionally representative cohort study of 1195 men aged 35–80 years at recruitment and living in the north-west regions of Adelaide, Australia. Hormonal profile was assessed in relation to
- Body composition, total and abdominal fat
- Muscle strength
- Life style factors

Clin Endocrinol (Oxf). 2009;71:261-72

The Florey Adelaide Male Ageing Study (FAMAS)

- Low TT was mostly associated with high abdominal fat and triglycerides and low muscle strength rather than ageing per se.
- Low BT was associated with increased age followed by high whole body fat percentage.
- BT and TT levels were higher in unmarried men and smokers.
- SHBG levels increased with age, but were also inversely associated with insulin and triglycerides.

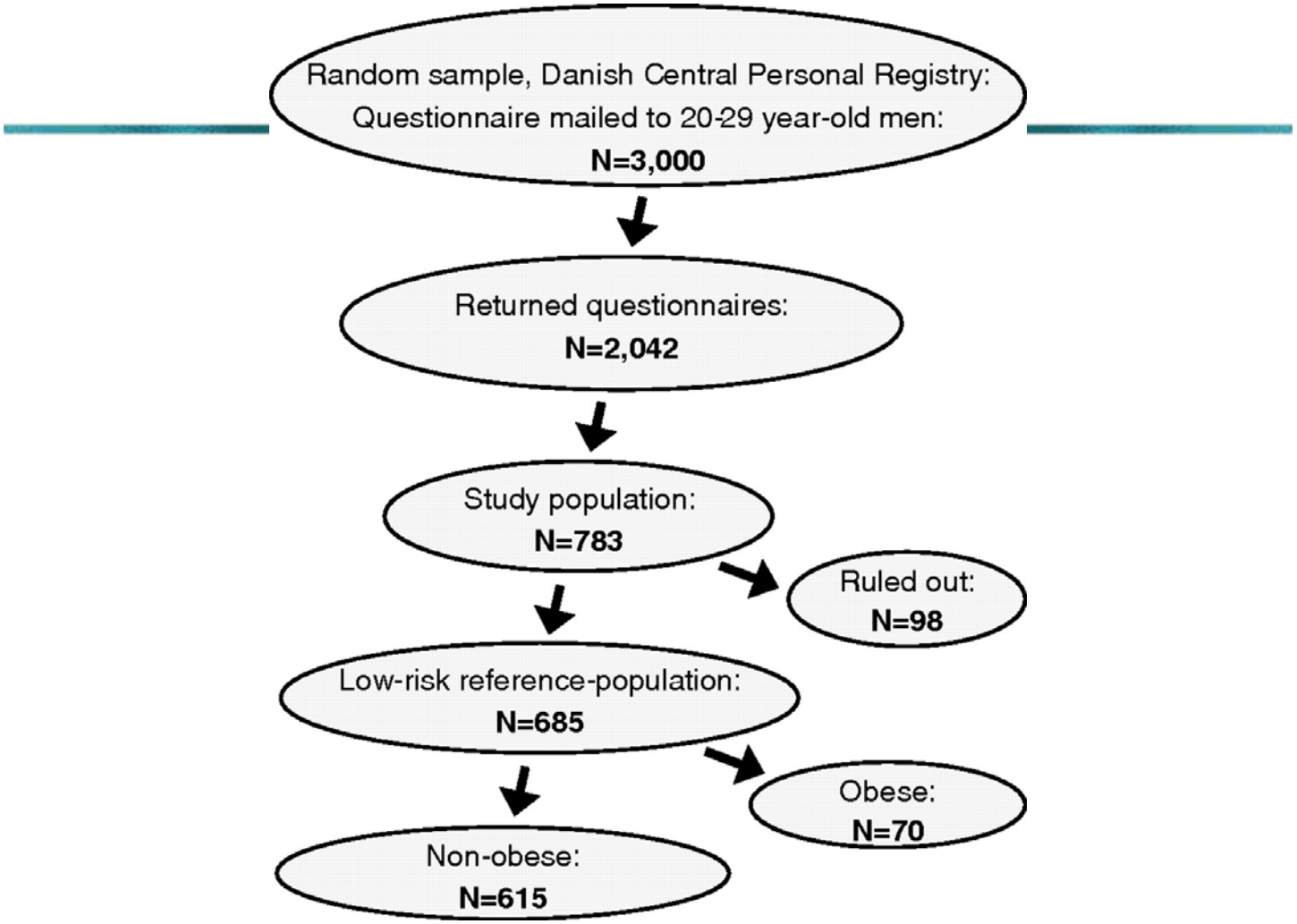
Clin Endocrinol (Oxf). 2009;71:261-72

The Florey Adelaide Male Ageing Study (FAMAS) (

- Increasing age was significantly associated with a decrease in BT and increase in SHBG,
- Increasing age had no significant association with TT ***when physical and lifestyle factors were simultaneously accounted for.***

Clin Endocrinol (Oxf). 2009;71:261-72

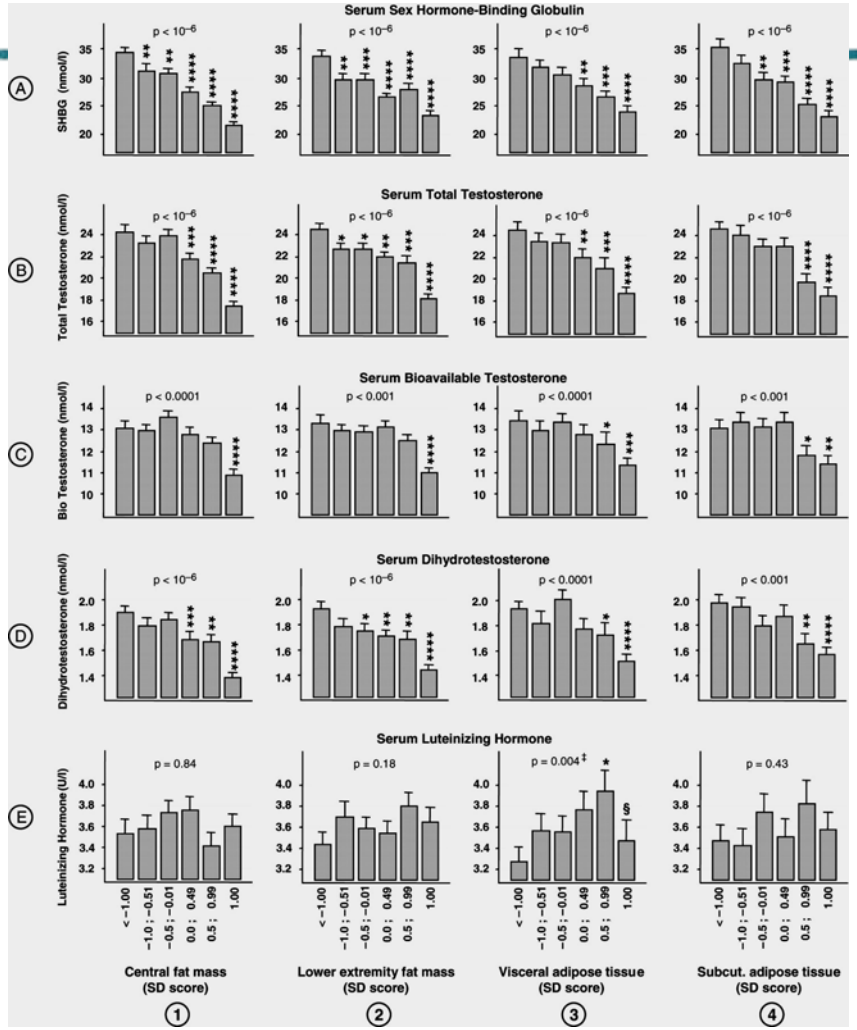
FIG. 1. Inclusion of the study population, establishment of the low-risk reference population, and division into healthy nonobese and obese men



Nielsen, T. L. et al. J Clin Endocrinol Metab 2007;92:2696-2705

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

FIG. 2. Serum SHBG (A), total testosterone (B), bioavailable testosterone (C), DHT (D), and LH (E) in 20- to 29-yr-old healthy men in relation to four fat depots: CFM assessed by DXA [column 1 (n = 685)]; LEFM assessed by DXA [column 2 (n = 685)]; visceral adipose tissue assessed by MRI [column 3 (n = 363)]; and sc adipose tissue assessed by MRI [column 4 (n = 363)]



Nielsen, T. L. et al. J Clin Endocrinol Metab 2007;92:2696-2705

THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

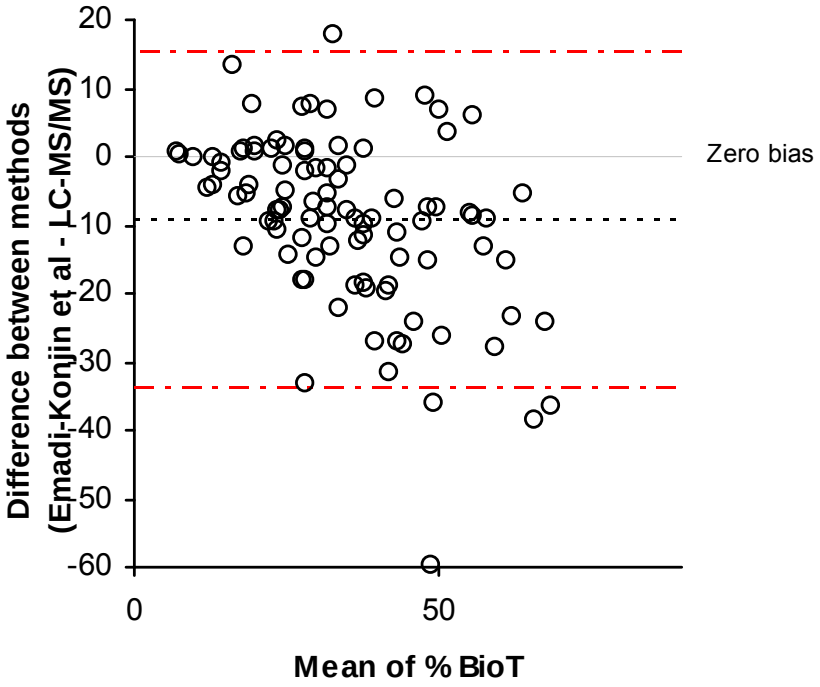
Visceral and Subcutaneous Adipose Tissue Assessed by Magnetic Resonance Imaging in Relation to Circulating Androgens, Sex Hormone-Binding Globulin, and Luteinizing Hormone in Young Men

- Total testosterone, bioavailable testosterone, free testosterone, DHT, and SHBG decline linearly with increasing CFM in young men.
- Visceral adipose tissues independently account for the decline in bioavailable testosterone and free testosterone
- In contrast, the decline in total testosterone and DHT with increased sc adipose tissue was secondary to decreased SHBG levels

Nielsen, T. L. et al. J Clin Endocrinol Metab 2007;92:2696-2705

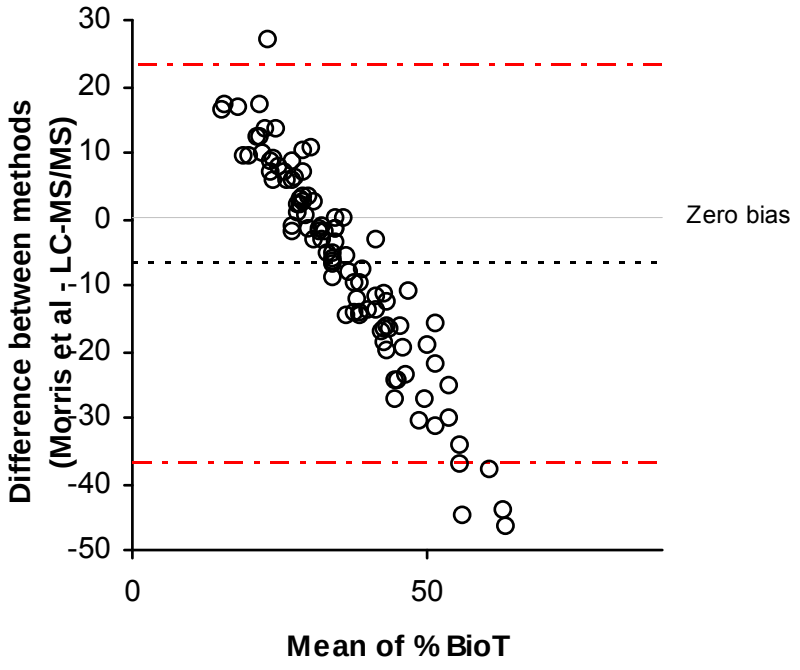
Results of comparison

Emadi-Konjin et al



Mean difference -9%

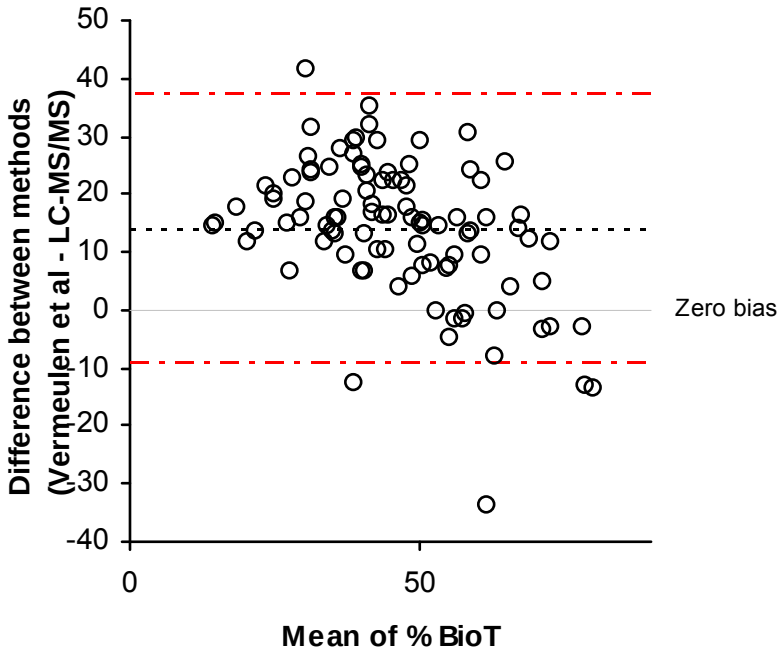
Morris et al



Mean difference -6%

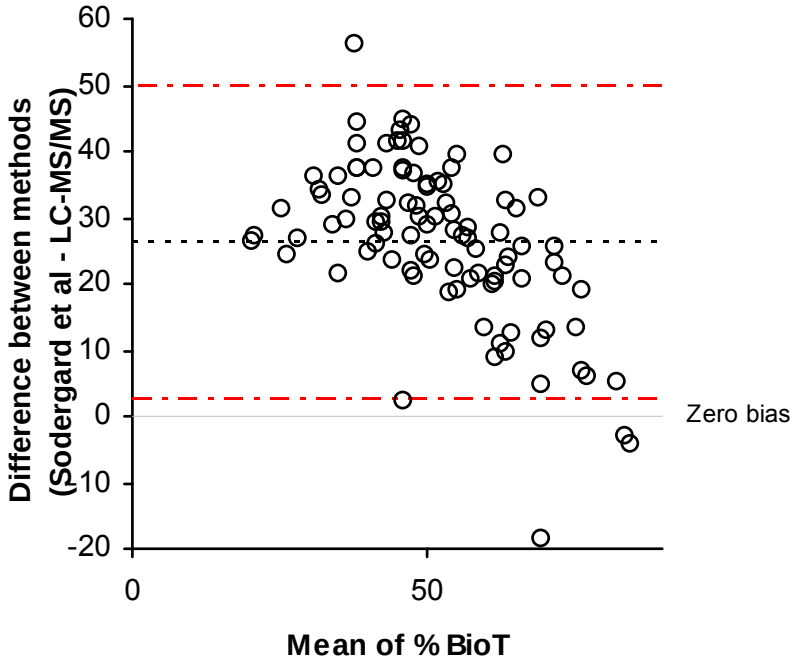
Results of comparison

Vermeulen et al



Mean difference +14%

Sodergard et al



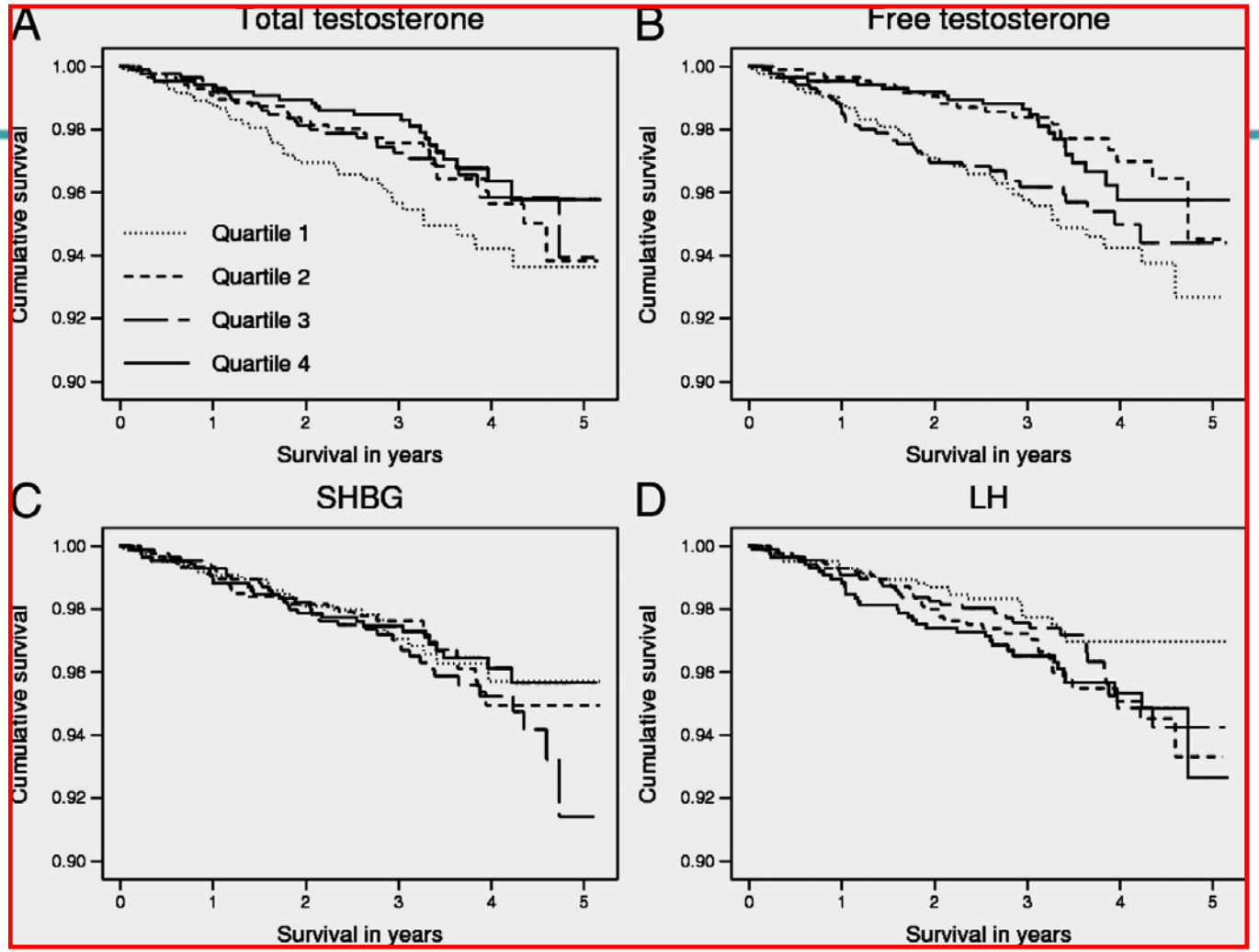
Mean difference +27%

The Age Related Decrease in Testosterone is Significantly Exacerbated in Obese Men With the Metabolic Syndrome

- Baseline total serum testosterone, lipid, glycemic and anthropometric data were obtained from 864 men (mean age 52 years) participating in 2 lipid treatment studies.
- Inclusion criteria for the 2 studies included low-density lipoprotein cholesterol 130 to 160 mg/dl and triglycerides 350 mg/dl or less.
- Mean baseline total serum testosterone levels in obese and severely obese aging men with the metabolic syndrome were around 150 and 300 ng/dl, respectively, less than that in aging, lean men with no metabolic syndrome.

Kaplan et al, J urol 176:1524, 2006

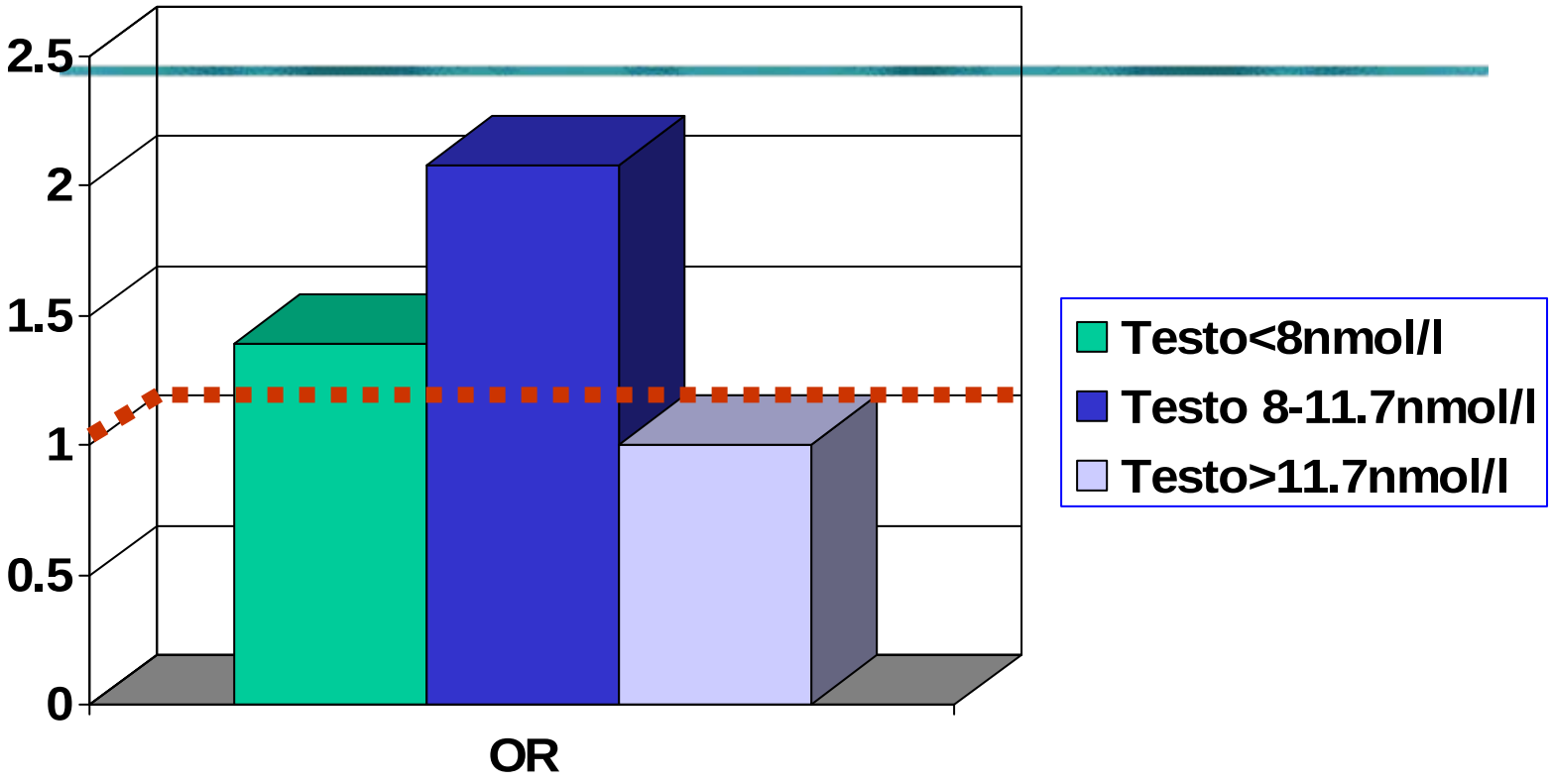
Kaplan Meier plots showing associations between baseline hormone levels (shown in quartiles) with stroke and TIA-free survival in community-dwelling older men



Yeap, B. B. et al. J Clin Endocrinol Metab 2009;94:2353-2359

The Journal of Clinical Endocrinology & Metabolism

Odds Ratio (OR) for incident stroke or TIA in men≥70y



3443 community-dwelling men ≥70 y/o

Yeap, B. B. et al. J Clin Endocrinol Metab 2009;94:2353-2359