AETC AIDS Education & Training Center Program Northeast/Caribbean

Primary Care and HIV: A Focus on Hypogonadism

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Disclosures

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The following planning members have no financial relationships to disclose: Cynthia Miller, MD, Sarah Walker, MS and Jennifer Price.

Disclosures

I have no financial relationships to disclose.

Goals and Objectives

- Outline the proper way to diagnose hypogonadism in male patients with and without HIV infection
- Describe the effects of testosterone replacement therapy
- Discuss potential side effects of testosterone replacement therapy

Polling Question 1

A male is found to have a low testosterone which is confirmed on repeat testing. The next step in the management of this patient is

A. HIV testing
B. **Determination of LH and FSH levels**
C. Determination of LH and FSH levels and a pituitary/hypothalamic MRI
D. Initiation of testosterone replacement therapy

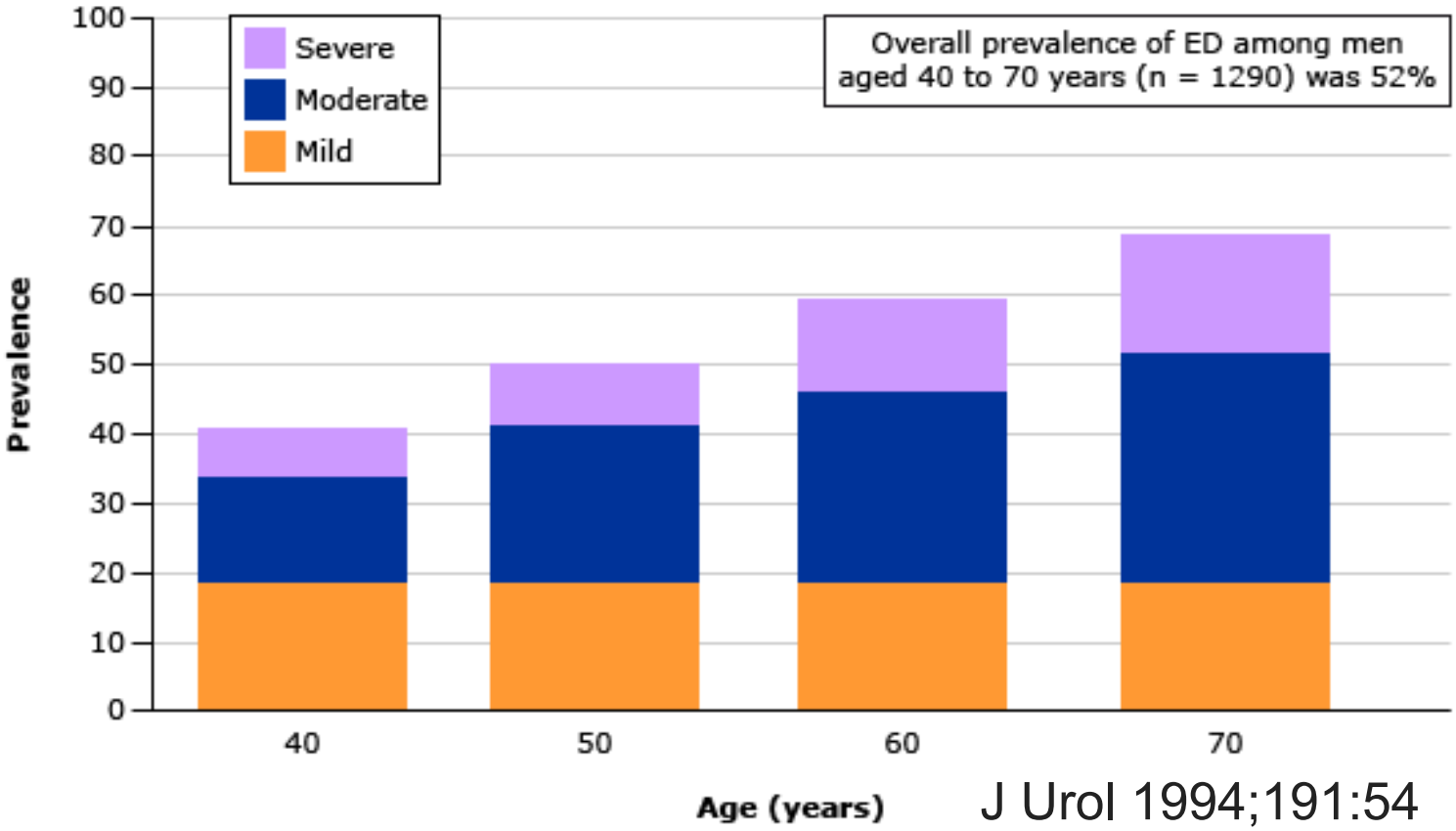
Case Presentation

- A middle-aged male presents for routine follow up but mentions that he is concerned about erectile function. He also reports generalized fatigue, though he is wondering if this is due to stress at work and age. He asks, “Doc, do I need testosterone? I hear it’ll help me perform better.”

Erectile Dysfunction

- The consistent or recurrent inability to acquire or sustain an erection of sufficient rigidity and duration for sexual intercourse

Prevalence and severity of ED in aging men in MMAS study



J Urol 1994;191:54

Case

- What is the general approach?
  - PDE_5 inhibitor therapy (sildenafil et al)
  - Reassure (and ignore)
  - Hypogonadism and/or ED questionnaire
  - Testosterone level

PDE_5 Inhibitors (e.g., sildenafil)

"Pfizer Inc.'s new impotence drug set a record for the most prescriptions written during its first week on the market, analysts said Monday, making the launch of Viagra the largest in history."

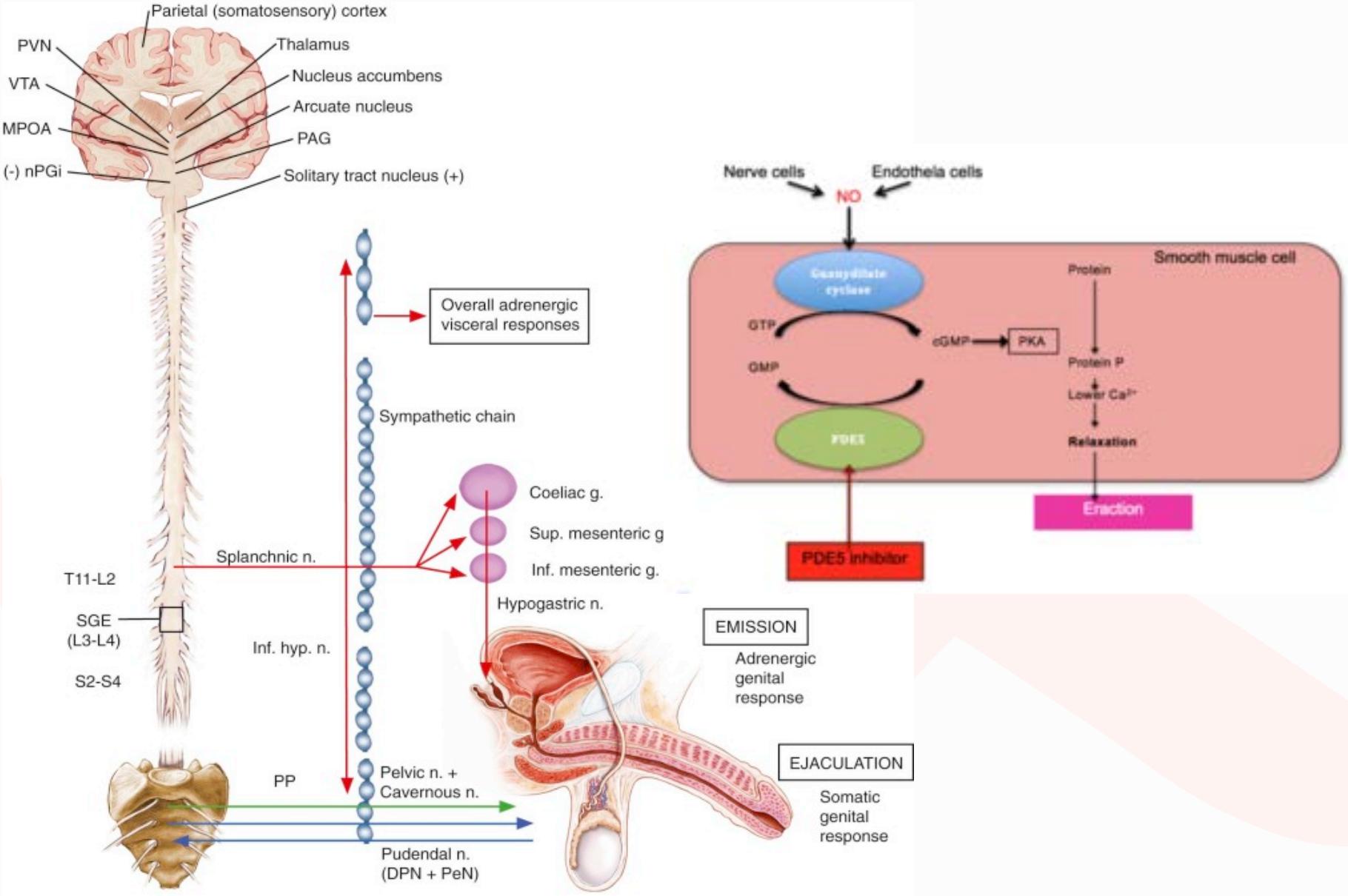
➢LA Times, April 21, 1998

Can we escape talking about Erectile Function??

Polling Question 2

What is it with those bathtubs?

A. They are trying to tell you that you need to be clean for the PGE_5 inhibitor to work
B. They are promoting safe sex by having the couple in separate bathtubs
C. There is no meaning whatsoever to the bathtubs
D. **The tubs are symbols of relaxing, taking your time, not hurrying, in that a bath is more relaxing than a shower.**



Jameson ed. Endocrinology: Adult and Pediatric Elsevier 2016

Erectile Dysfunction

- In addition to age, the best predictors of ED are diabetes mellitus, hypertension, obesity, dyslipidemia, cardiovascular disease, smoking, and medication use. Obstructive sleep apnea is also a risk factor for ED

Jameson ed. Endocrinology: Adult and Pediatric Elsevier 2016

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Regular Intercourse Protects Against Erectile Dysfunction: Tampere Aging Male Urologic Study

Juha Koskimäki, MD, PhD,[a] Rahman Shiri, MD, PhD,[b] Teuvo Tammela, MD, PhD,[a] Jukka Häkkinen, MD, PhD,[a] Matti Hakama, ScD,[b] Anssi Auvinen, MD, PhD[b]

[a]Tampere University Hospital, Department of Urology, Tampere, Finland; [b]University of Tampere, School of Public Health, Tampere, Finland.

"Regular intercourse has an important role in preserving erectile function among elderly men, whereas morning erection had no association. Continued sexual activity decreases the incidence of erectile dysfunction in direct proportion to coital frequency."

The American Journal of Medicine (2008) 121, 592-596

Countess: *You are a great lover!*
Boris: *I practice a lot when I'm alone.*
-- "Love and Death" 1975

Case

- What is the general approach?
  - PDE_5 inhibitor therapy (sildenafil et al)
  - Reassure (and ignore)
  - Hypogonadism and/or ED questionnaire
  - Testosterone level

Reassure and Ignore

- Of course never ignore your patient!
- Reassurance may be all that is needed
  - This can always be reassessed!

Case

- What is the general approach?
  - PDE_5 inhibitor therapy (sildenafil et al)
  - Reassure (and ignore)
  - Hypogonadism and/or ED questionnaire
  - Testosterone level

ADAM Questionnaire

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased "enjoyment of life"
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noticed a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

Endocrine Society Clinical Practice Guideline

CLINICAL PRACTICE GUIDELINE

Testosterone Therapy in Men With Hypogonadism: An Endocrine Society* Clinical Practice Guideline

Shalender Bhasin,[1] Juan P. Brito,[2] Glenn R. Cunningham,[3] Frances J. Hayes,[4] Howard N. Hodis,[5] Alvin M. Matsumoto,[6] Peter J. Snyder,[7] Ronald S. Swerdloff,[8] Frederick C. Wu,[9] and Maria A. Yialamas[10]

JCEM 2018;103:1715-1744

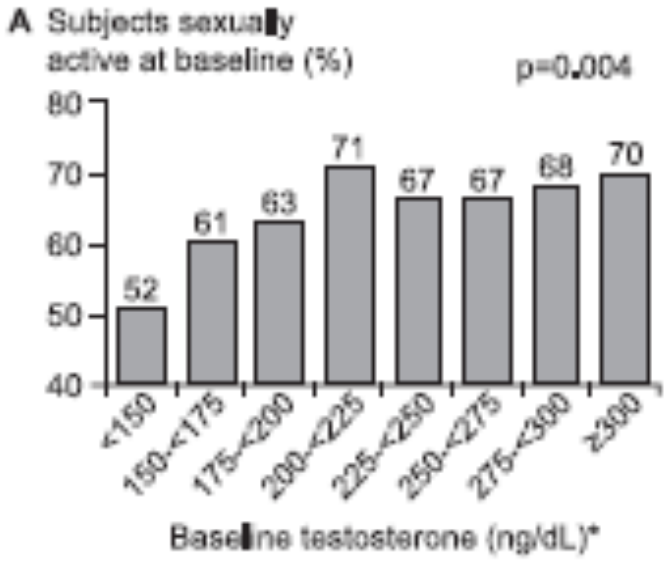
Case Finding Questionnaires (including ADAM)

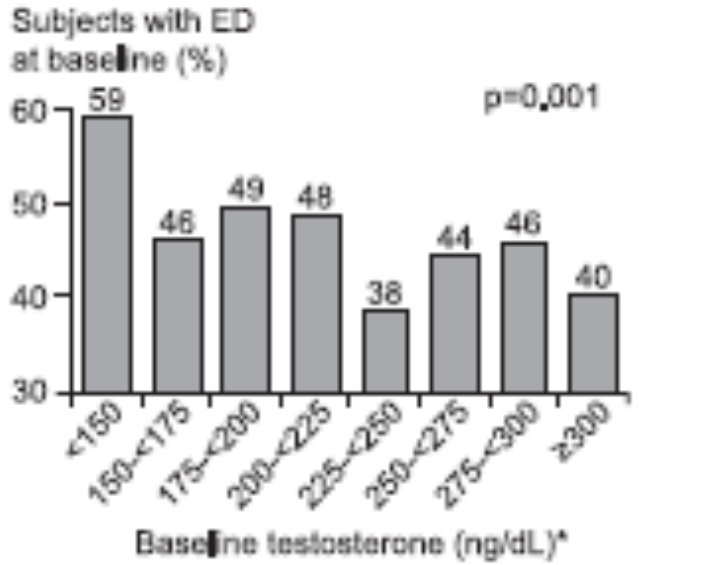
- "Limited information about the performance properties…" "Therefore, we suggest clinicians not use the available case finding questionnaires for detecting T deficiency."

JCEM 2018;103:1715-1744

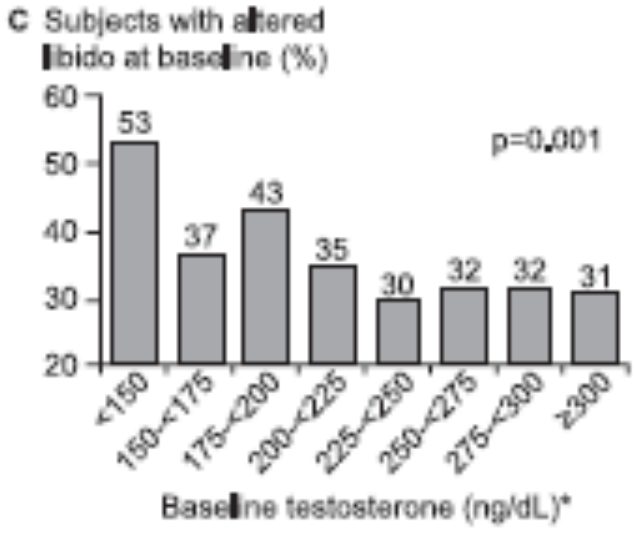
Case

- What is the general approach?
  - PDE_5 inhibitor therapy (sildenafil et al)
  - Reassure (and ignore)
  - Hypogonadism and/or ED questionnaire
  - Testosterone level





Testosterone levels and sexual function



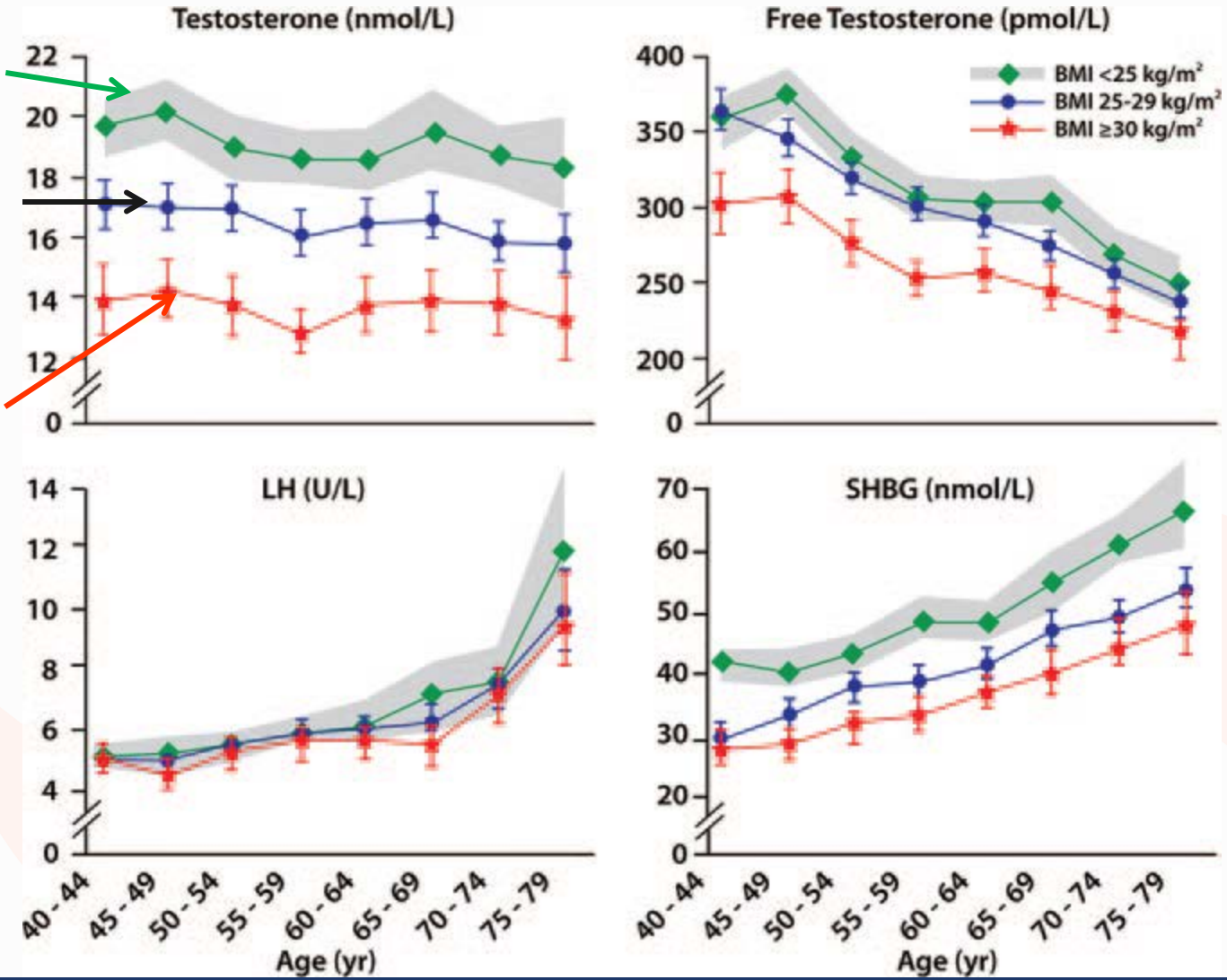
JCEM 91:1323–1328, 2006

European Male Aging Study

BMI < 25

BMI 25-30

OBESE



JCEM 2006;93:2737

Table 4. Conditions in Which There Is a High prevalence of Low T Concentrations and for Which We Suggest Measurement of Serum T Concentrations

Pituitary mass, radiation to the pituitary region, or other diseases of the sellar region
Treatment with medications that affect T production or metabolism, such as opioids and glucocorticoids
Withdrawal from long-term AAS use
HIV-associated weight loss
Infertility
Osteoporosis or low trauma fracture
Low libido or erectile dysfunction

JCEM 2018;103:1715-1744

Measuring Testosterone: --not as easy as we hope--

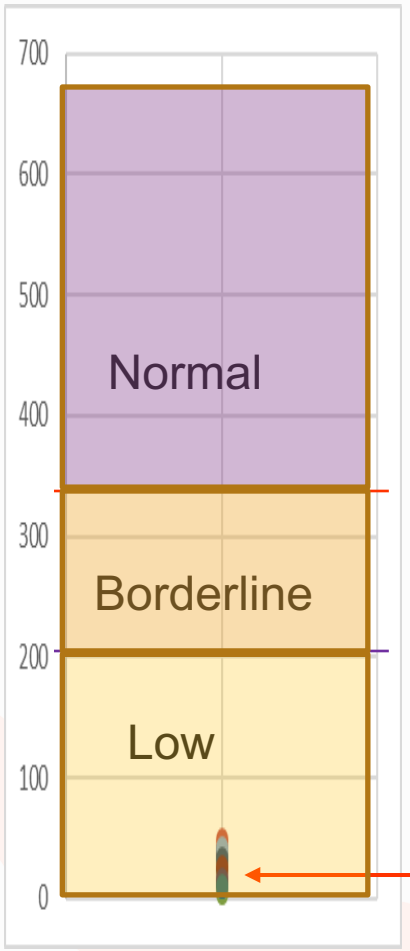
- Reliable assay (liquid chromatography-tandem mass spectrometry is the best, but is more expensive and not routine)
- Diurnal variation
- “Free” versus total levels

Polling Question 3

What method of testosterone measurement is routinely done for your patients?

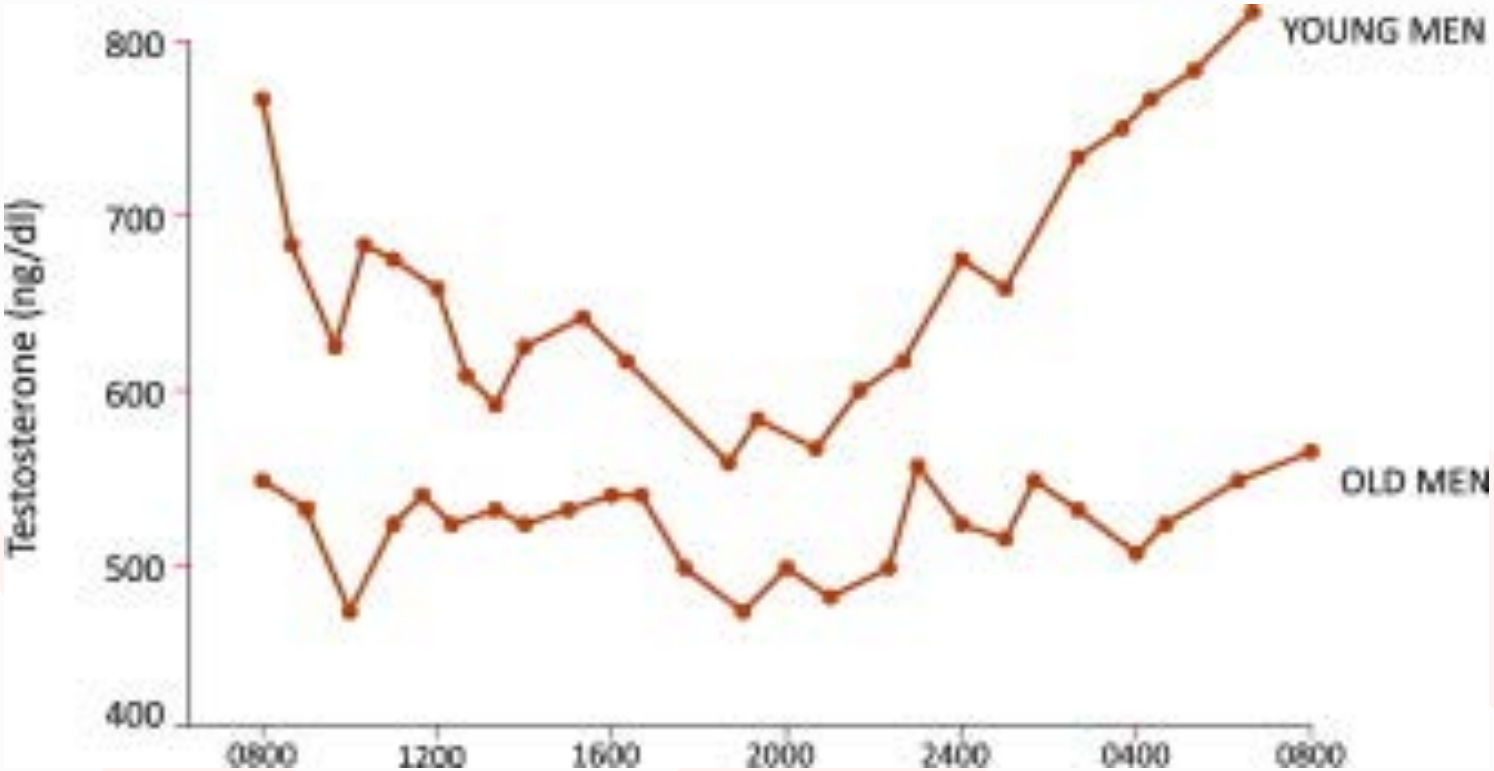
A. Liquid chromatography-tandem mass spectrometry
B. A commercially available immunoassay kit
C. An assay certified by the CDC Hormone Standardization Program for Testosterone
D. I haven't the slightest clue

Testosterone Assay Normal Values



- In 2013, AMC Endocrinology and Clinical Chemistry reviewed the AMC CLIA assay performance and established these levels for men. This assay could not determine reliable norms for children and females.

Testosterone: Age and Time of Day



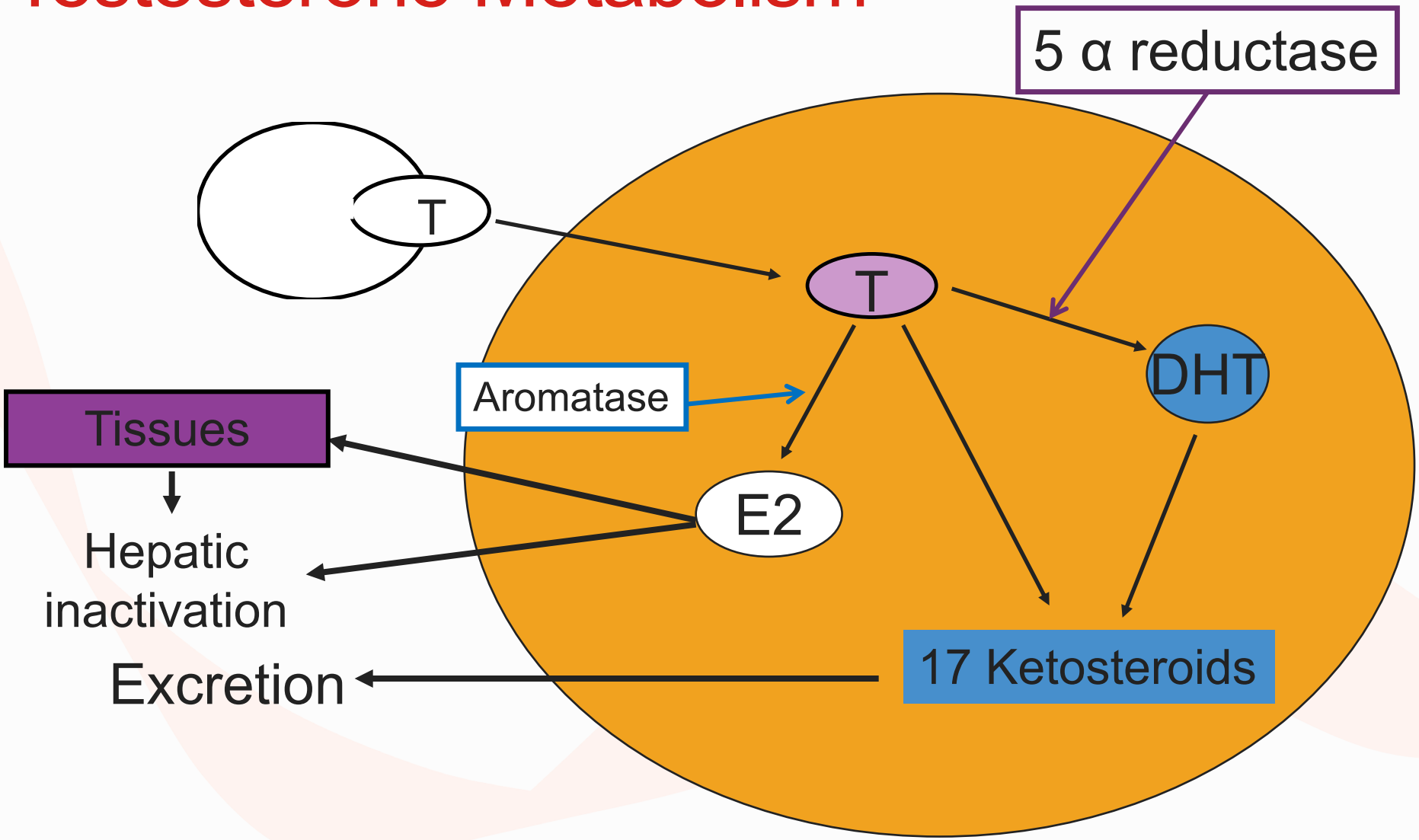
J Clin Endocrinol Metab 1983;56:1278–81

Endocrine Society Recommendations: Testosterone Measurement

"Clinicians should measure total testosterone concentrations on two separate mornings when the patient is fasting…and should use an accurate and reliable method."

What About Free Testosterone?

Testosterone Metabolism



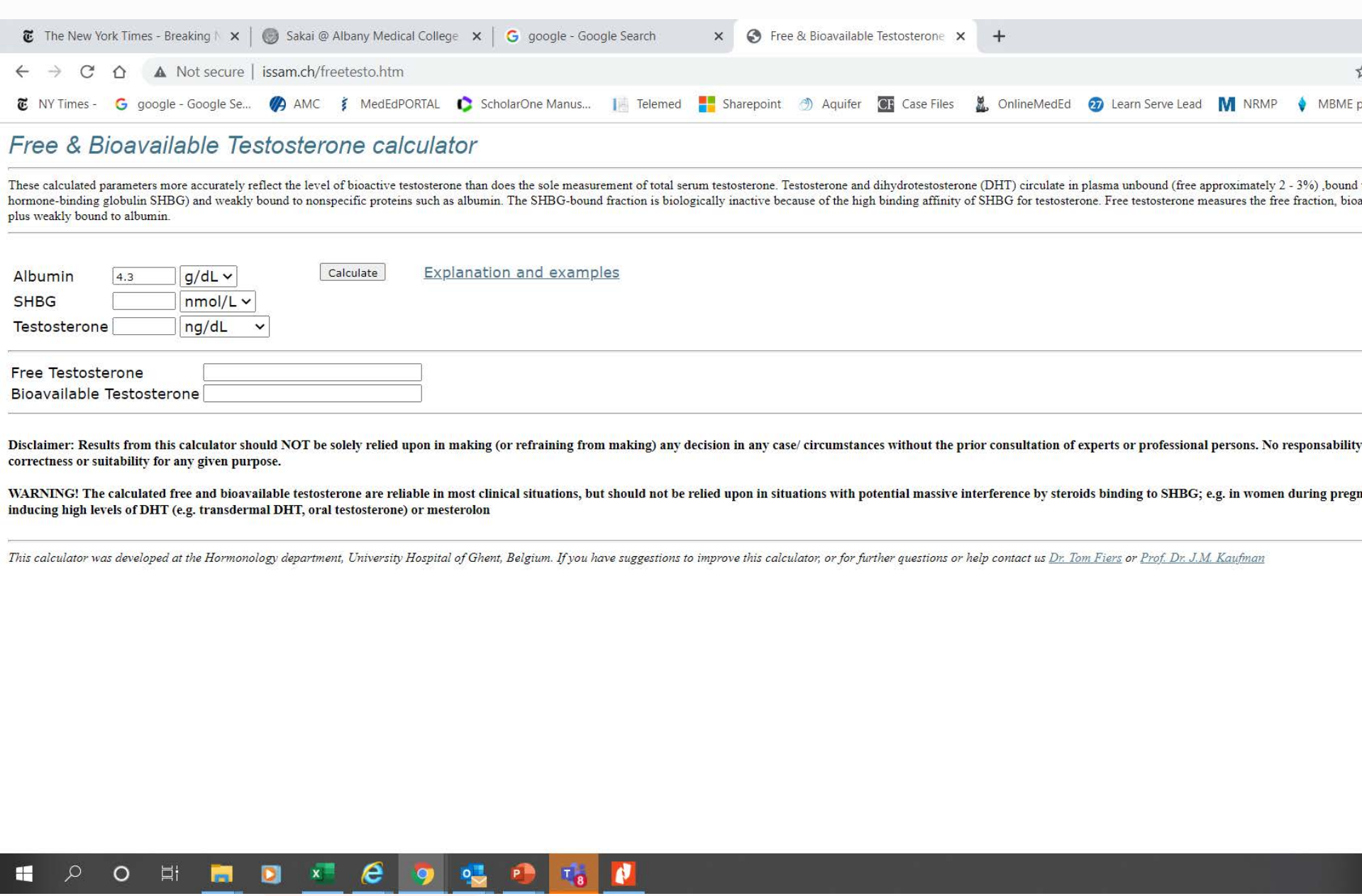
What About Free Testosterone?

- Consider when SHBG can be altered
- *Caveat: most FT levels calculate from total T, so if that assay is not reliable, neither is FT. Best: use equilibrium dialysis. Do not use analog based FT assays*

Table 2. Conditions in Which Measurement of FT Concentration Is Recommended

1. Conditions that are associated with decreased SHBG concentrations
Obesity
Diabetes mellitus
Use of glucocorticoids, some progestins, and androgenic steroids
Nephrotic syndrome
Hypothyroidism
Acromegaly
Polymorphisms in the SHBG gene
2. Conditions associated with increased SHBG concentrations
Aging
HIV disease
Cirrhosis and hepatitis
Hyperthyroidism
Use of some anticonvulsants
Use of estrogens
Polymorphisms in the SHBG gene
3. Total testosterone concentrations in the borderline zone around the lower limit of the normal range (*e.g.*, 200-400 ng/dL)

Adapted with permission from Bhasin *et al.* (8).



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
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, bioa
plus weakly bound to albumin.

Albumin 4.3 g/dL
SHBG nmol/L
Testosterone ng/dL

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
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 pregn
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

HIV and Hypogonadism

- "Wasting syndrome in AIDS: pathophysiologic mechanisms and therapeutic approaches"
  - Weinroth SE, et al. *Infect Agents Dis*. 1995 Jun;4(2):76-94
- "Effects of Potent Antiretroviral Therapy on Free Testosterone Levels and Fat-Free Mass in Men in a Prospective, Randomized Trial: A5005s, a Substudy of AIDS Clinical Trials Group Study 384"
  - *Clinical Infectious Diseases*, Volume 45, Issue 1, July 2007

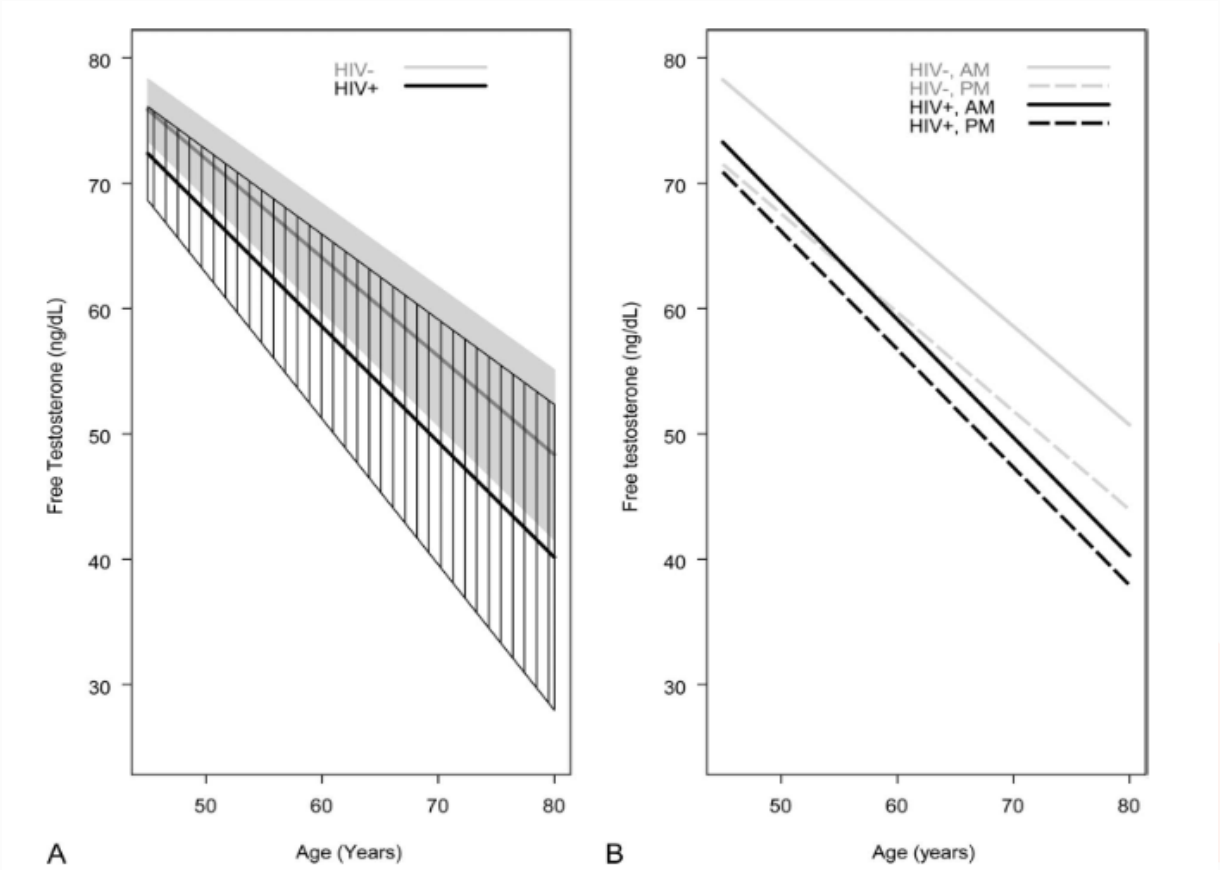
Where Are We in 2021?

- HIV has become a chronic comorbidity with an (almost) normal life expectancy
- Multicenter AIDS Cohort Study (MACS) found a rate of hypogonadism of 24.5 in HIV+ versus 7.8% in HIV- individuals*
- SHBG levels appear to be higher in treated HIV+ patients, with no explanations

*Monroe AK, et al HIV Med. 2012;13:358–366.

MACS: Longitudinal Free T levels

- 10 year follow up
- 182 HIV+ vs. 267 HIV- individuals
- Mean age 48.8



J Acquir Immune Defic Syndr Volume 71, 2016

Multicenter German 50/2010 Study

- 322 Men > 50
- Three arms: HIV+; HIV- with DM; HIV- without DM
- Testosterone deficiency defined as calculated Free T < 65 pg/mL
- Hypogonadism defined as testosterone deficiency and positive Aging Male Symptoms Survey.

Exp Clin Endocrinol Diabetes. Published online: 2021-01-21

Results

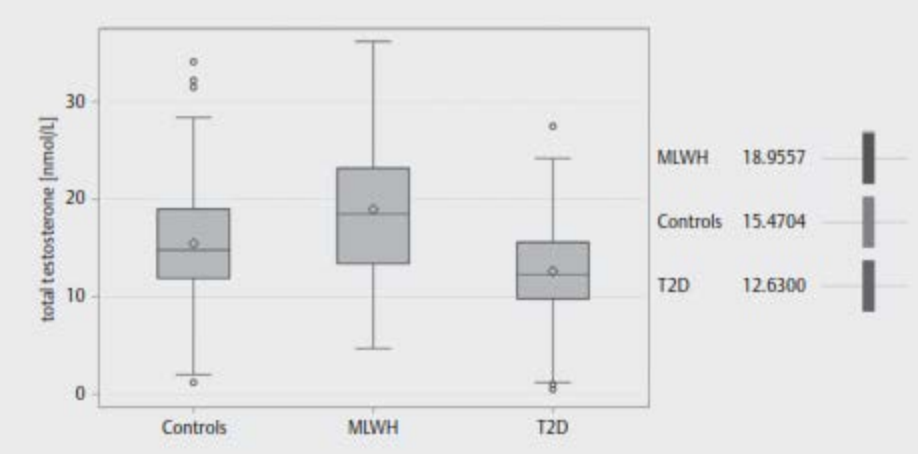
	Controls	MLWH	Diabetes
Testosterone Deficiency	34.5%	35.0%	44.9%
Hypogonadism	3.5%	7.7%	14.3%

Postel et al. Functional Hypogonadism and Testosterone Deficiency in Aging Males With and Without HIV-infection. *Experimental and Clinical Endocrinology & Diabetes*; eFirst

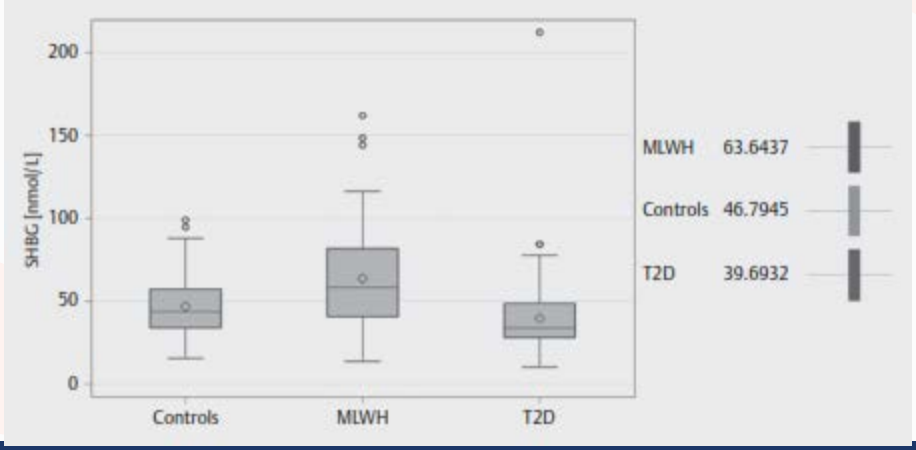
Results

Controls MLWH DM

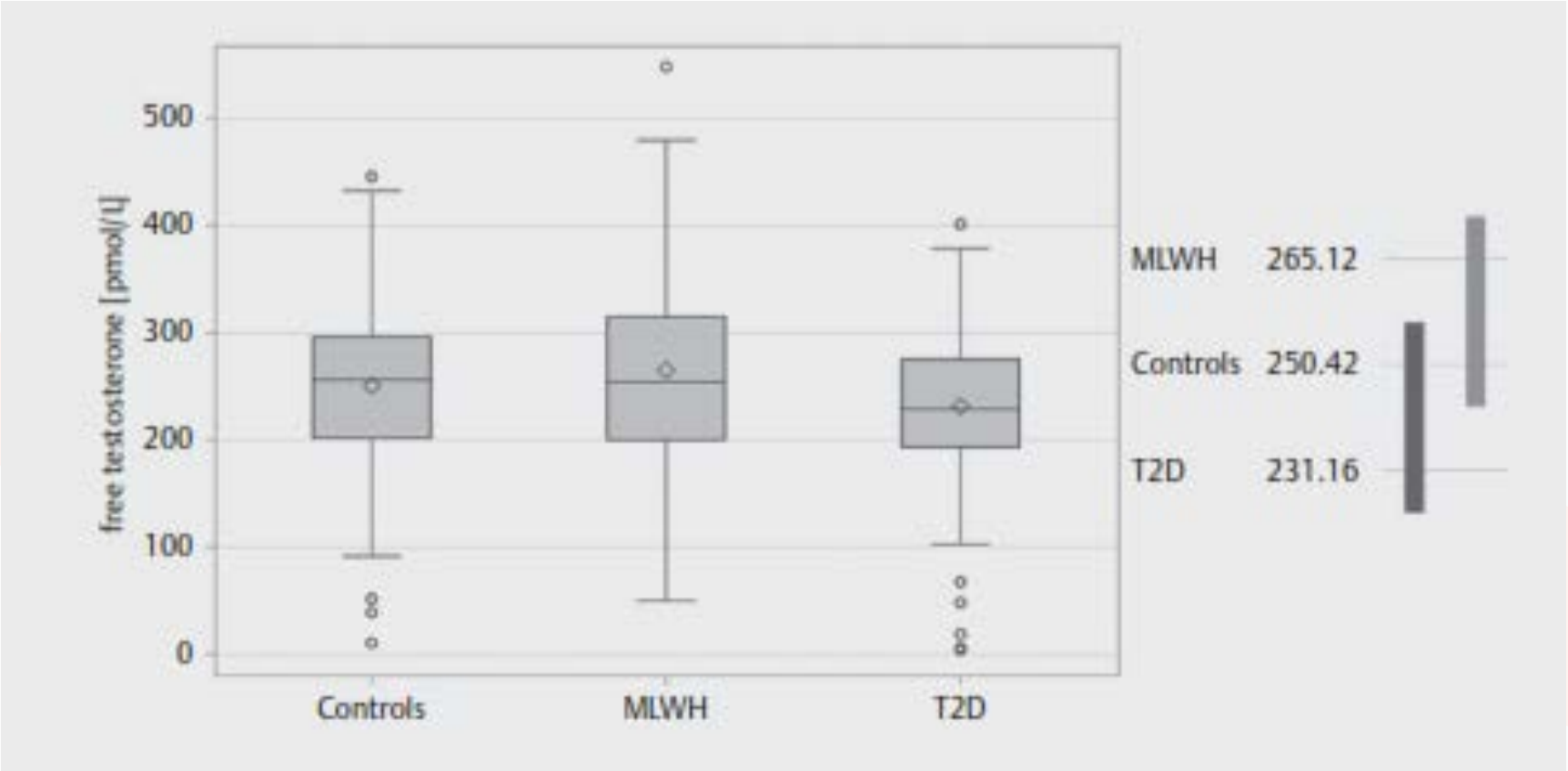
Total T



SHBG



Results



Postel et al. Functional Hypogonadism and Testosterone Deficiency in Aging Males With and Without HIV-infection. *Experimental and Clinical Endocrinology & Diabetes*

Hypogonadism and DM

- Up to 30% of patients with DM may have hypogonadism[1]
- Meta review (43 studies) found testosterone levels on average were 76 ng/ml lower in men with DM than those without[2]

1. Diabetes Care 2011;34(8):1854–9.
2. Ding et al., JAMA. 2006;295(11):1288

Diagnosis of Hypogonadism (Endo Society)

- Diagnosis requires consistent and unequivocally* low free or total testosterone levels and the presence of symptoms.

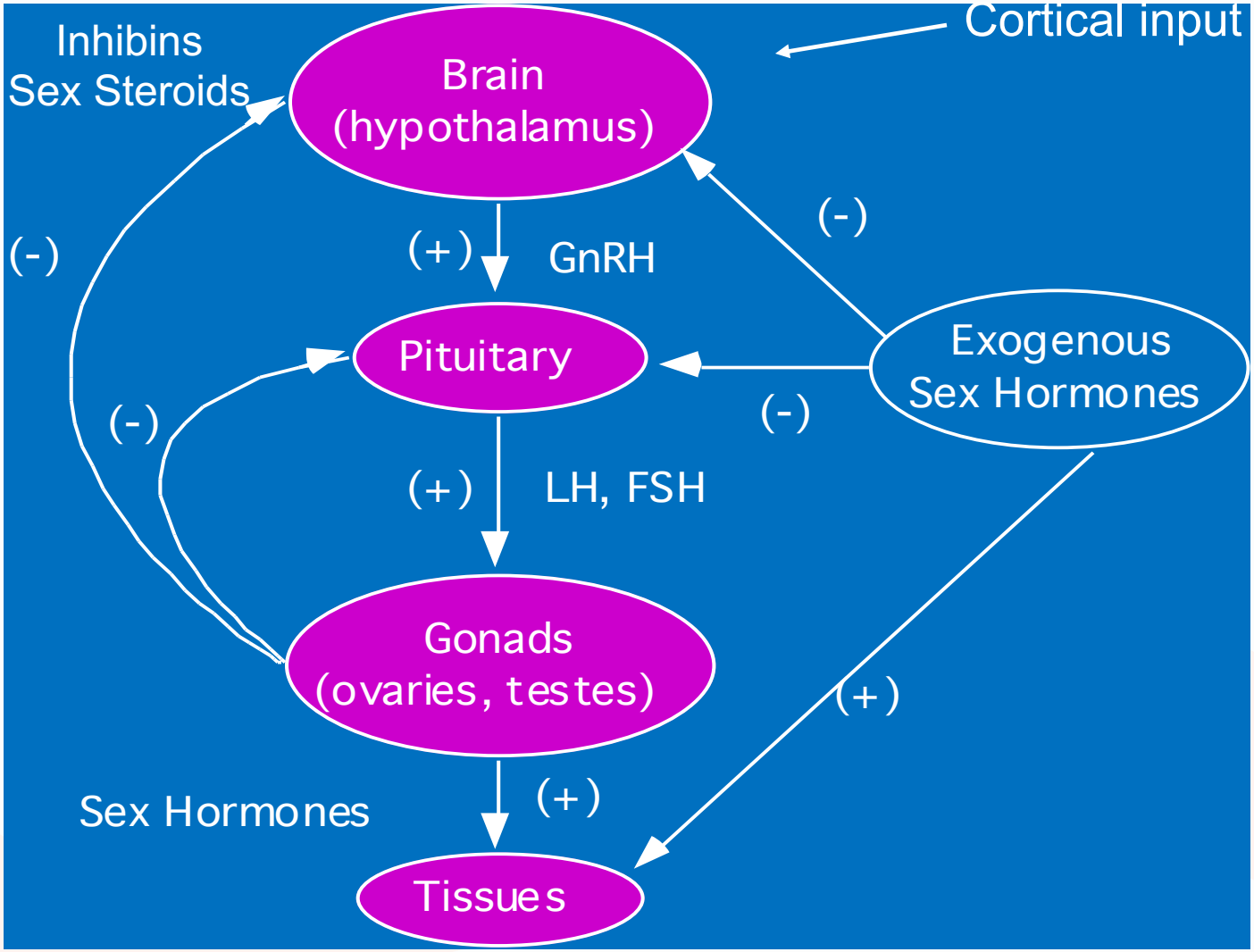
* Good assay, no recent illness, etc.

JCEM 2018;103:1715-1744

What next?

- Determine the etiology: is it primary hypogonadism or secondary (“Hypogonadotropic”) hypogonadism

HPG Axis


Cortical input
Inhibins
Sex Steroids
Brain
(hypothalamus)
(-)
(+)
GnRH
(-)
Pituitary
Exogenous
Sex Hormones
(-)
(-)
(+)
LH, FSH
Gonads
(ovaries, testes)
(+)
Sex Hormones
(+)
Tissues

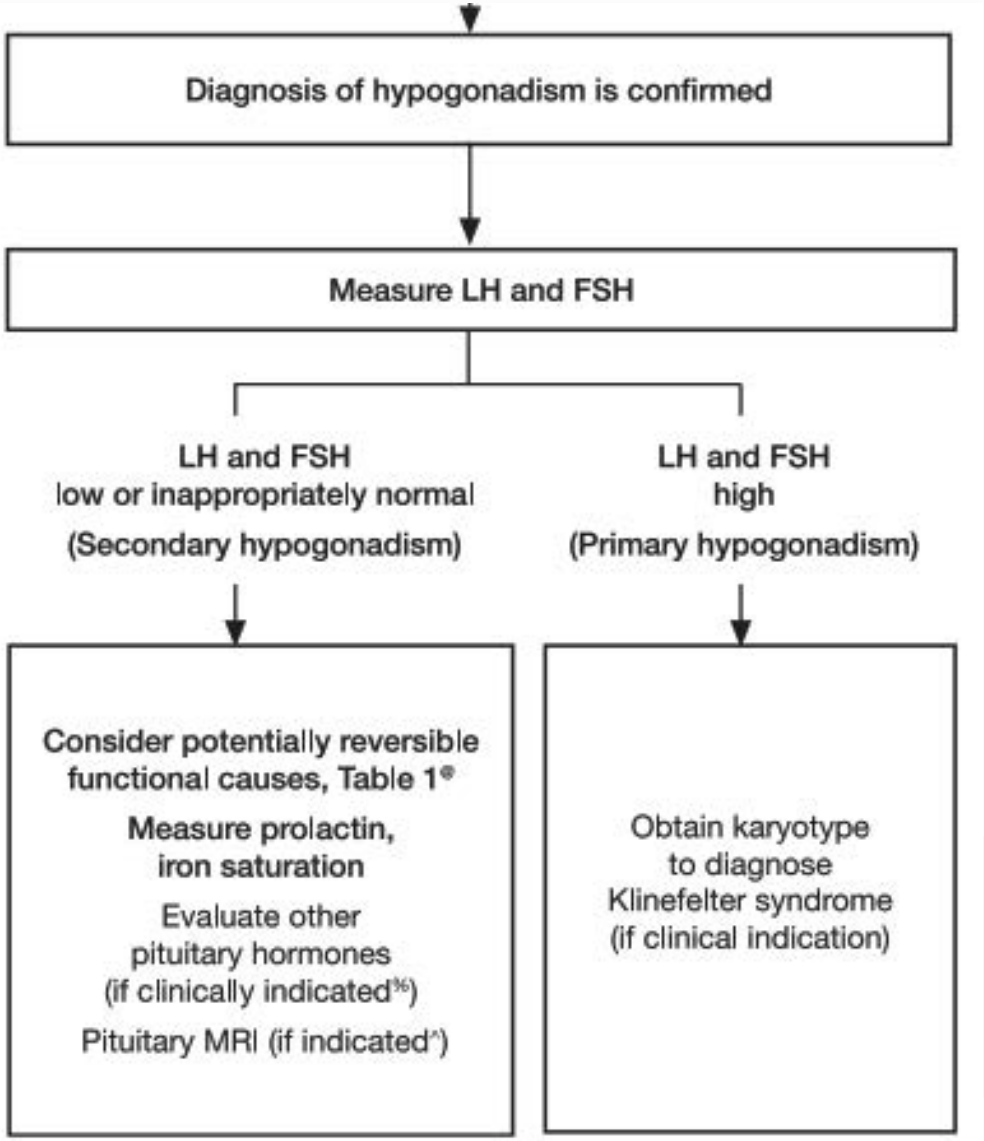


Table 1. Classification of Hypogonadism and Causes of Primary and Secondary Hypogonadism

Primary Hypogonadism	Secondary Hypogonadism
ORGANIC	
KS	Hypothalamic/pituitary tumor
Cryptorchidism, myotonic dystrophy, anorchia	Iron overload syndromes
Some types of cancer chemotherapy, testicular irradiation/damage, orchidectomy	Infiltrative/destructive disease of hypothalamus/pituitary
Orchitis	Idiopathic hypogonadotropic hypogonadism
Testicular trauma, torsion	
Advanced age	
FUNCTIONAL	
Medications (androgen synthesis inhibitors)	Hyperprolactinemia
End-stage renal disease[a]	Opioids, anabolic steroid use, glucocorticoids
	Alcohol and marijuana abuse[a]
	Systemic illness[a]
	Nutritional deficiency/excessive exercise
	Severe obesity, some sleep disorders
	Organ failure (liver, heart, and lung)[a]
	Comorbid illness associated with aging[a]

[a]Combined primary and secondary hypogonadism, but classified to usual predominant hormonal pattern. Adapted with permission from Bhasin *et al.* (7).

JCEM 2018;103:1715-1744

Pituitary MRI?

"Surveys of middle-aged and older men with secondary hypogonadism and sexual dysfunction have revealed a low prevalence of hypothalamic–pituitary abnormalities.

…(consider) performing this procedure (MRI) in men with panhypopituitarism, persistent hyperprolactinemia, serum TT < 150 ng/dL or symptoms of tumor mass effect (e.g., visual impairment, visual field defect, or new onset headache)."

Testosterone Therapy

Rancho Bernardo Study

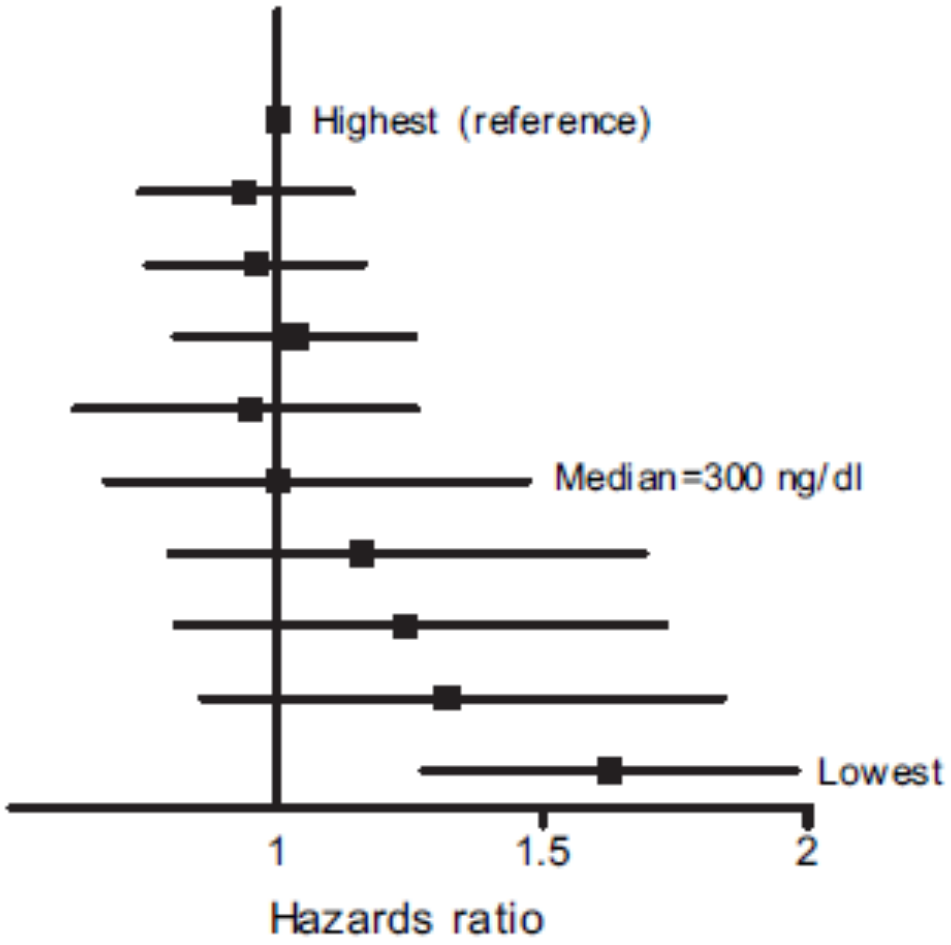


FIG. 1. All-cause mortality according to deciles of total testosterone adjusting for age, BMI, waist to hip ratio, current smoking, alcohol use, and exercise. The *squares* represent point estimates for HRs, the *lines* indicate 95% CIs. The median total testosterone values for deciles 1–10 were 171, 209, 241, 266, 288, 314, 338, 370, 422, and 507 ng/dl, respectively.

JCEM 93: 68–75, 2008

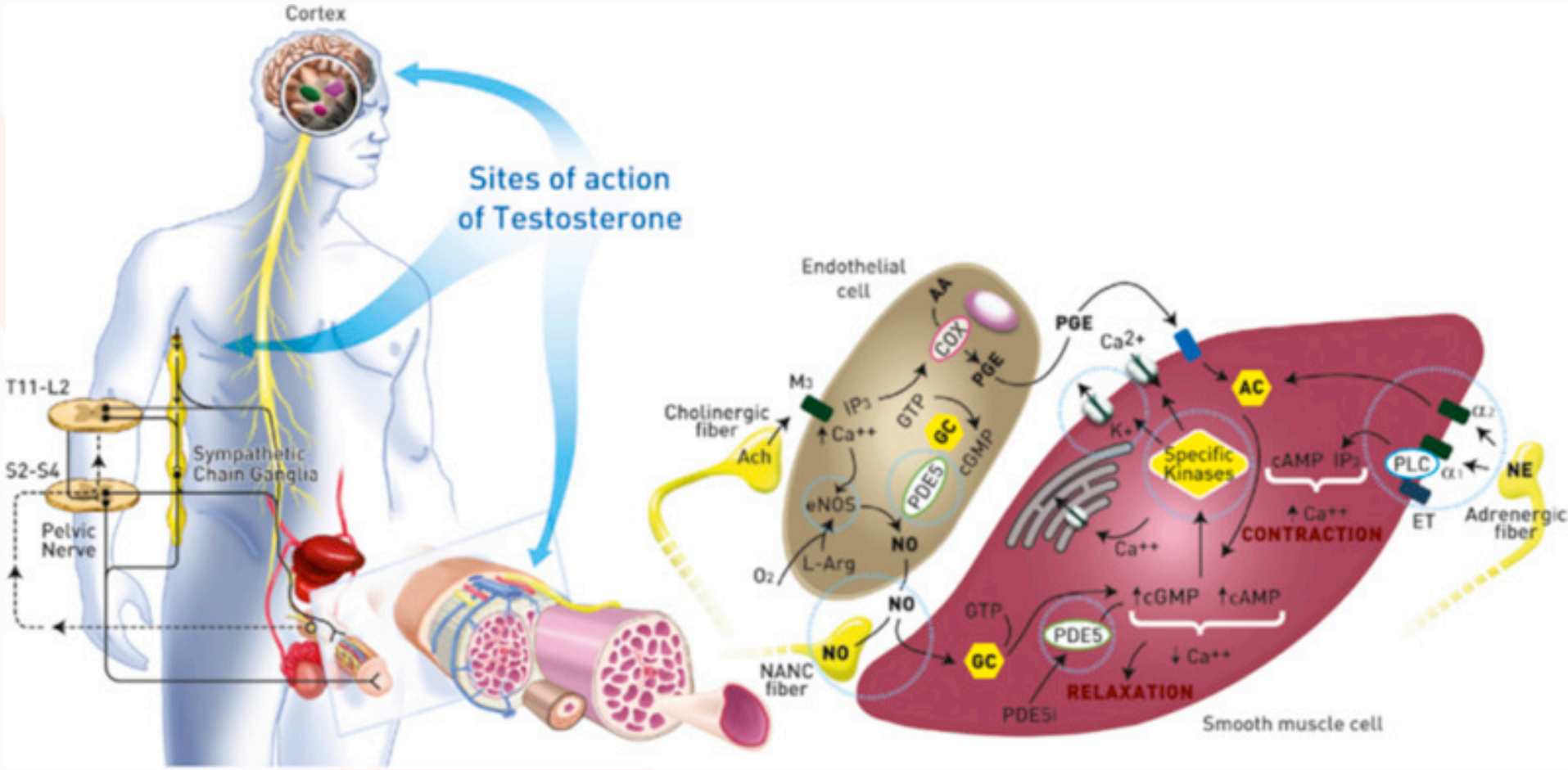
Polling Question 4

A man without testicles (and not receiving testosterone) *cannot* get erections

A. True

B. False

Testosterone and Erectile Function

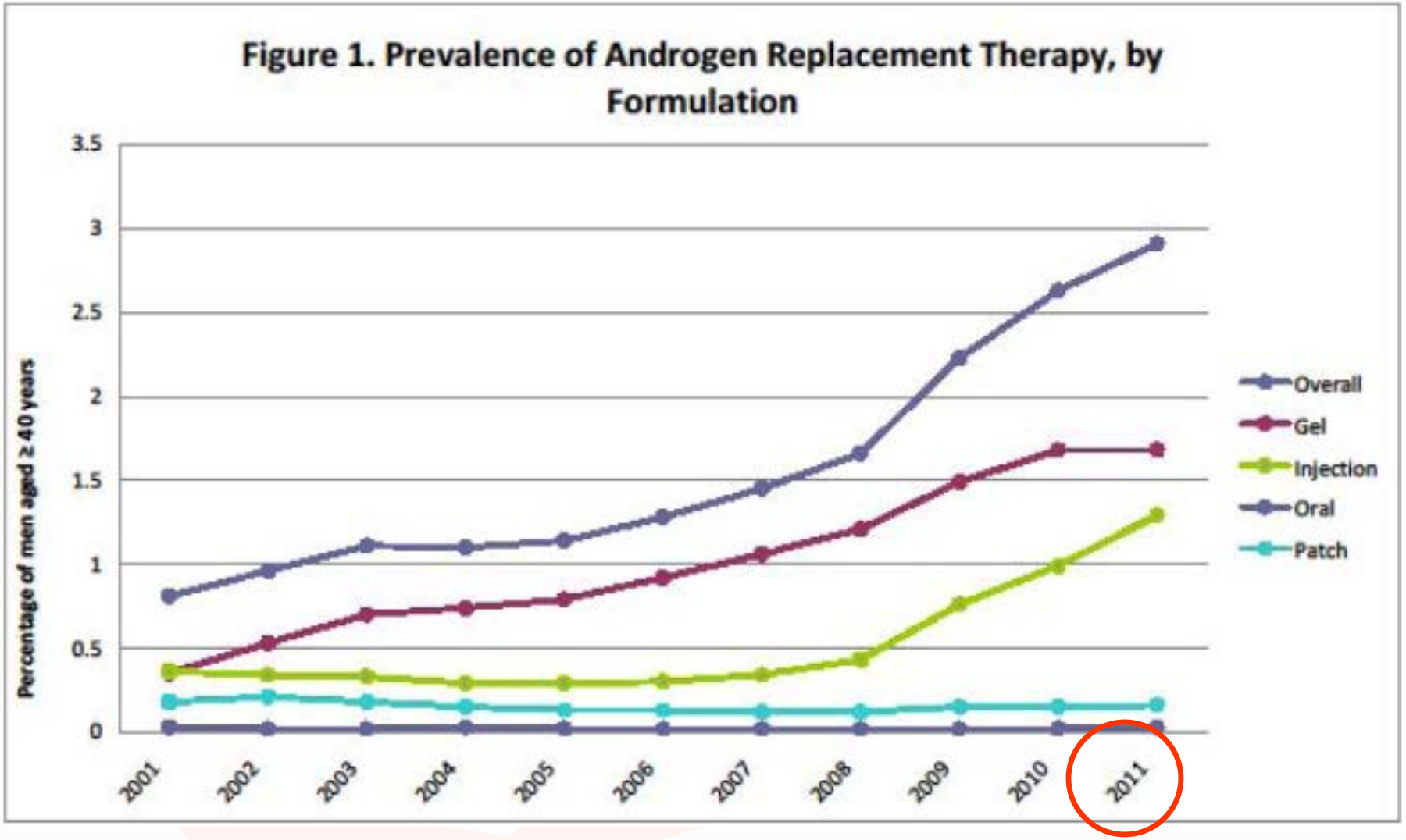


Jameson ed. Endocrinology: Adult and Pediatric Elsevier 2016

Testosterone Therapy

- EBM For hypogonadal men (T < 300):
  - Statistically significant, clinically mild improvements in libido and erectile function
  - Increased lean muscle mass, decreased fat mass: for older men, +/- improved fatigue
  - Minor improvements in mood, no discernable benefit to cognitive function

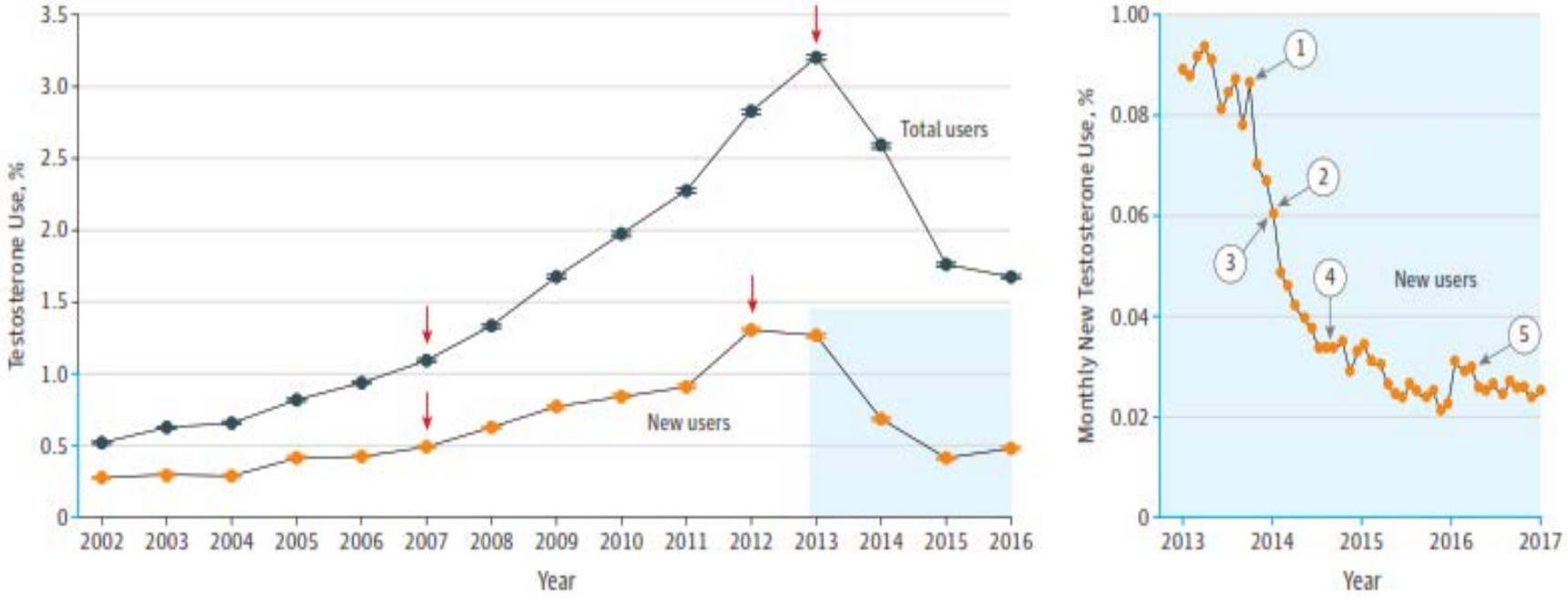
JCEM 2018;103:1715-1744



JAMA Intern Med. 2013;173(15):1465-1466

But Then Something Happened

Figure 1. Total and New Testosterone Use Among Men 30 Years or Older in the United States, 2002-2016



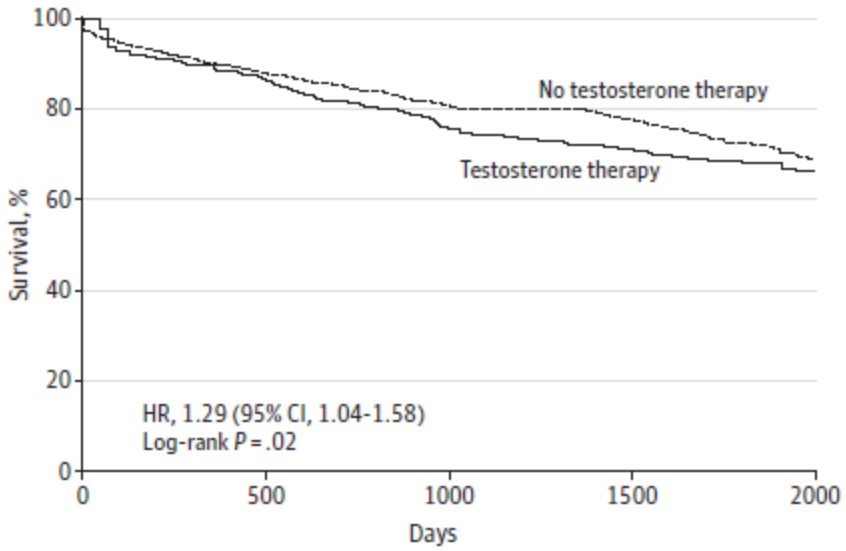
JAMA 2018;320:200-202

Vigen et al (JAMA)

JAMA. 2013;310(17):1829-1836

- Reported a hazard ratio of 1.29

Figure 2. Kaplan-Meier Survival Curves With Testosterone Therapy Evaluated as a Time-Varying Covariate



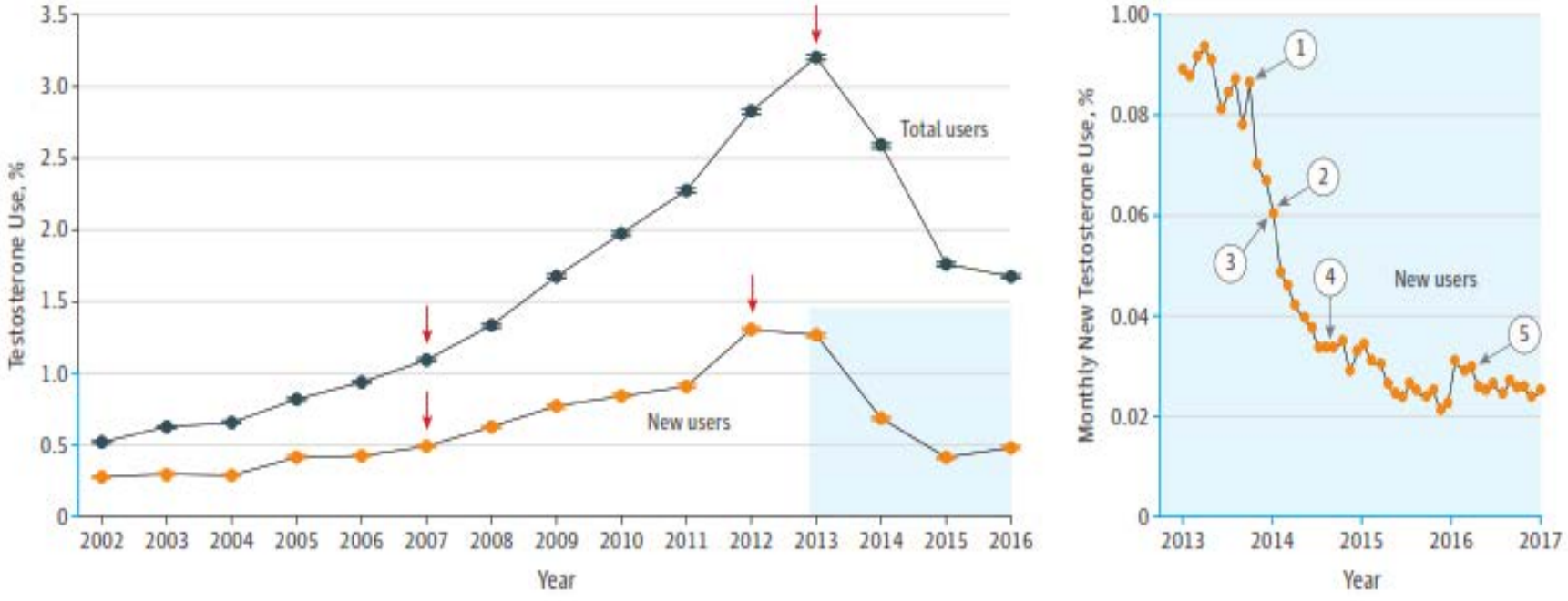
No. at risk					
Testosterone therapy					
No	8709	5337	2897	918	206
Yes	0	439	500	233	61

Testosterone and ASCD

- With much conflicting data, the FDA stated "..the studies presented in the petition have significant limitations that weaken their evidentiary value for confirming a causal relationship.."
- But the FDA did require drug makers to change labeling. The European Medicines Agency did not (2014)

Testosterone and CV Harm?

Figure 1. Total and New Testosterone Use Among Men 30 Years or Older in the United States, 2002-2016



3: FDA communication: 4: FDA advisory committee
5: FDA label change

JAMA 2018;320:200-202

Endocrine Society Guidelines: Testosterone and CV Risks

- Insufficient RCTs to answer the question
- “Most meta-analyses have not shown a significant association betwee T treatment and CV events, MACE, or deaths”

JCEM 2018;103:1715-1744

Testosterone: Adverse Effects

- Cardiovascular effects?
- Erythrocytosis (Hct > 54%): can be seen, more common in older men.
- Reduced fertility
- Growth of metastatic prostate cancer

JCEM 2018;103:1745-1754

Testosterone and Prostate

- “There is no strong evidence for the association between prostate cancer risk and T concentrations”
- “However,…T administration promotes the growth of metastatic prostate cancer…we recommend against T supplementation in men with prostate cancer and suggest assessing prostate cancer risk prior to treatment.”

JCEM 2018;103:1745-1754

Testosterone and Prostate

- “T therapy does not worsen lower urinary tract symptoms (LUTS) in men who do not have severe LUTS prior to treatment.”
- “We do not know whether T worsens LUTS in men who have severe LUTS at baseline, because such men have been excluded from T trials.”

ES Guidelines: Summary

- Diagnosis of Hypogonadism: *ONLY* in men with signs and symptoms and *unequivocally* and *consistently* low serum total and/or free T concentrations
- Recommend *against* routine screening in the general population
- Distinguish between primary and secondary causes

J Clin Endocrinol Metab 2018;103:1715-1744

ES Guidelines: Summary

- Recommend T therapy in hypogonadal men
  - *Caveats:* men planning fertility; breast or prostate cancer; palpable prostate nodule or PSA > 4; ↑ Hct; untreated sleep apnea; severe LUTS; recent MI or stroke; uncontrolled heart failure

ES Guidelines: Summary

- T therapy For Older Hypogonadal Men (55-69)
  - “Discuss potential benefits and risks” (specifically prostate)
  - Men over 65: suggest against routinely prescribing T therapy in men with low T. If symptoms are present, individualize
- Monitoring
  - If PSA > 1.4 ng/mL increase, or value > 4.0, urologic consultation

Summary and Final Thoughts

- Treating associated conditions is probably best (diabetes, obesity, narcotic use) but hardest
- HIV positive patients require special consideration in establishing the diagnosis of hypogonadism

Post-test Polling Question (A repeat of question 1)

A male is found to have a low testosterone which is confirmed on repeat testing. The next step in the management of this patient is

A. HIV testing
B. **Determination of LH and FSH levels**
C. Determination of LH and FSH levels and a pituitary/hypothalamic MRI
D. Initiation of testosterone replacement therapy

HIV - HCV - PrEP - PEP
Clinical Consultations
For Providers in Upstate NY

Call or E-mail for a consultation:
518-262-6864
Monday – Friday 8:00 a.m. – 4:30 p.m.
prokopw@amc.edu

If you have experienced an occupational exposure such as a needle stick, please call 518-262-4043. You will be given an opportunity on the telephone menu to speak to a physician 24 hours a day.

www.amc.edu/hiv