Male Menopause: Disease or Pseudoscience?


AMA Morning Rounds

Today's medical news prepared *exclusively* for you

AMA AMERICAN MEDICAL ASSOCIATION

In affiliation with BulletinHealthcare

Good Morning **Dr. William Winter**. Here are today's top stories. Wednesday, March 4, 2015

Leading the News

FDA to require warning on labels of testosterone products.

USA Today (3/4, Szabo) reports on Tuesday the US Food and Drug Administration announced it will require manufacturers of prescription testosterone therapy "to include a warning about health risks on product labels," and the agency advised men using such products to "contact a doctor if they develop symptoms of heart attack or stroke."

The New York Times (3/4, A16, Tavernise, Subscription Publication) reports that two studies suggesting an association between testosterone use and heart problems prompted the FDA to reassess the safety of the products last year, and a panel of independent experts "voted overwhelmingly in September that the labels should be changed to reflect the heart risks." In a statement, the FDA said "We are requiring that the manufacturers of all approved prescription testosterone products change their labeling to clarify the

March 4, 2015 story:

FDA to require warning on labels of testosterone products.

William E. Winter, MD
University of Florida
Departments of Pathology and Pediatrics

4-27-2015

Learning objectives: At the conclusion of this presentation, the laboratorian will be able to:

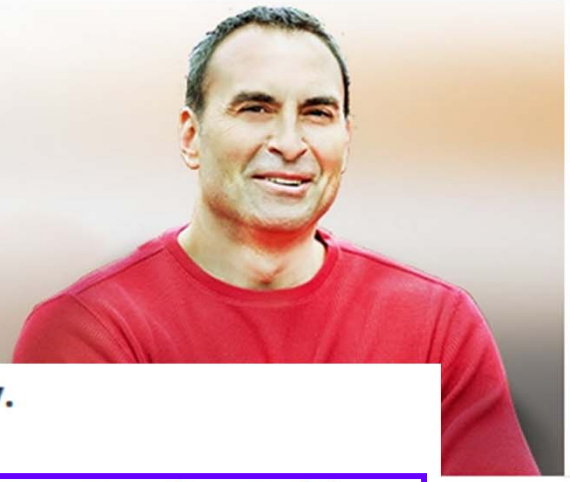
1. List the forms of testosterone (T) that circulate.
2. Explain how total and free T are best measured.
3. Describe how free T falls with advancing age.
4. Recall the symptoms of late-onset hypogonadism.
5. Diagnose late-onset hypogonadism.
6. Anticipate the clinical demand for T testing.
7. Explain the risks of T replacement.
8. Plan appropriate monitoring for men treated w/ T.
9. Discuss the benefits and risks of T replacement tx.

Low T Center

HOME | ABOUT US | PROCESS | LOCATIONS | FAQ | ARTICLES | NEWS | CONTACT US | CAREERS

It is time to get back in the game.

Take control of your quality of life. You can recapture your youth and vitality!



Lear

Low Testosterone? Get Diagnosed and Start Treatment Today.

It's been estimated that over 13 million men suffer from low testosterone (Low T), and most of them don't even know it.

Instead they endure the ever worsening symptoms of fatigue, lowered drive and libido, steady weight gain and loss of mental clarity as if it were an accepted part of aging. The physicians at Low T Center utilize medical laboratory testing and evaluations to determine whether the real problem is actually low testosterone – which is sterone replacement therapy..

urban DICTIONARY

Time to man up. Stop

Want to restore the ener a pounds you've been gaining? St ind—and youthful vigor, too. Most

To fulfill your responsibilites as a man, despite your insecurities and constant ability to place yourself in embarrasing and un-manly scenarios.

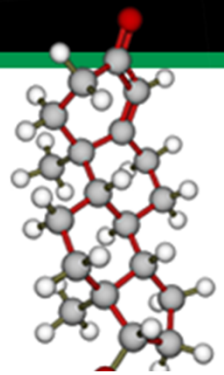
Note: Slides w/ blue backgrounds are not shown.

Symptoms of Low T

- ✔ Fatigue
- ✔ Decreased motivation/drive
- ✔ Decreased mental clarity
- ✔ Increased body fat
- ✔ Decreased libido

Read more

Causes of Low T



- ✔ Natural process of aging
- ✔ Chronic Illness
- ✔ Use of certain medications
- ✔ Trauma
- ✔ Other less common conditions

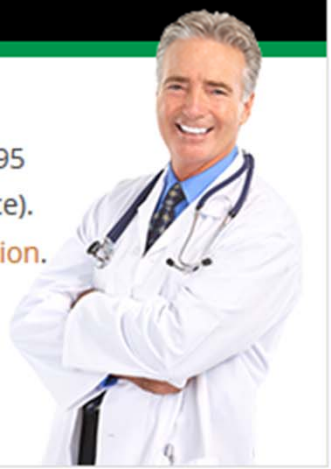
Read more

Cost of Treatment

Most insurance accepted.

Inclusive treatment costs $395 per month (without insurance).

Click here for more information.



Verify Insurance

Testosterone results in 45 minutes!

Gentlemen, restart your engines!

The Low T Center process offers a quick and easy way to diagnose and treat low testosterone. Your testosterone levels will be tested during your initial visit in our in-house laboratory. The test takes just a few minutes and will be performed by the professional medical staff dedicated to helping you get your quality of life back.

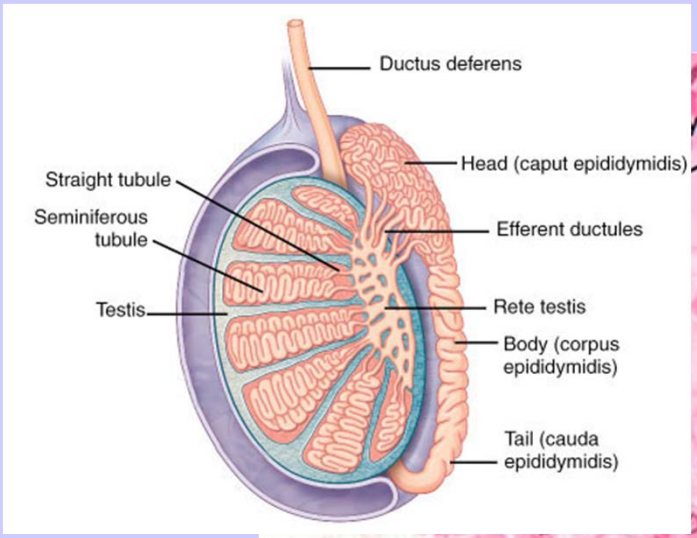
You will have your test results in 45 minutes or less. If your test indicates your testosterone levels are below clinically acceptable, the medical professionals at the Low T Center will discuss your individual treatment options.

Low T Center

Consent for Testosterone Replacement Therapy

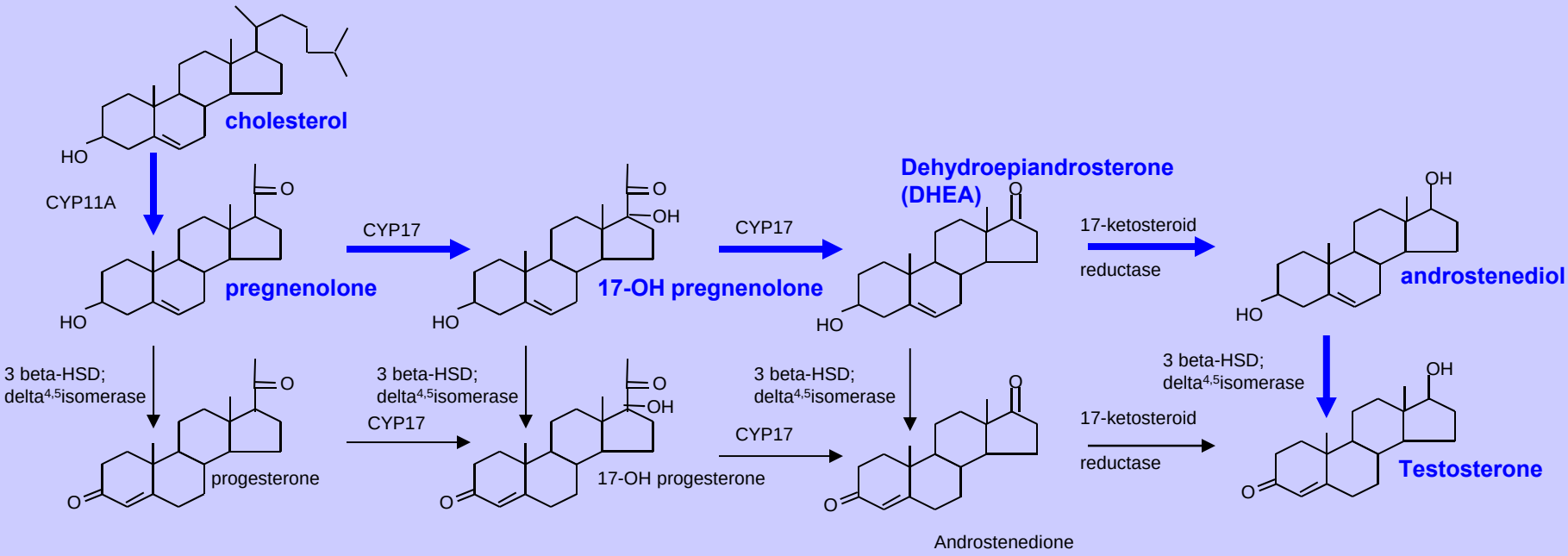
Side effects may include increased red blood cells, acne, sleep apnea, breast enlargement, testicular atrophy, lowered sperm count, mood swings, injection site reactions such as bleeding, pain, swelling, redness, or infection, increased estrogen production, or fluid retention. TRT is not recommended for patients who have breast or prostate cancer, or who are thinking about becoming parents. You should also be aware that some recent studies have associated TRT with increased risk for adverse cardiovascular events, such as blood clots, heart attacks, or strokes, in certain types of patients.

Where is testosterone synthesized in the body?



A = Leydig cell, B = spermatozoa, C = primary spermatocyte, D = spermatogonium

How is testosterone synthesized in the body?



The testes and adrenal cortex share several pathways of steroid synthesis. The production of testosterone predominantly involves the ^{5}delta-pathway (pregnenolone -- > 17-hydroxy pregnenolone -- > DHEA -- > androstenediol) over the ^{4}delta-pathway (progesterone -- > 17-hydroxy progesterone -- > androstenedione -- > testosterone).

What are the effects of testosterone in utero in 46,XY fetuses?

- **Development of normal male internal and external genitalia**

- **"Androgenization" of brain**

"Studies over the last 50 years have verified that prenatal androgens have permanent effects in rhesus monkeys on the neural circuits that underlie sexually dimorphic behaviors. *These behaviors include both sexual and social behaviors, all of which are also influenced by social experience. Many juvenile behaviors such as play, mounting, and vocal behaviors are masculinized and/or defeminized, and aspects of adult sexual behavior are both masculinized (e.g. approaches, sex contacts, and mounts) and defeminized (e.g. sexual solicits)."*

Thornton J, Zehr JL, Loose MD. Effects of prenatal androgens on rhesus monkeys: a model system to explore the organizational hypothesis in primates. Horm Behav. 2009 May;55(5):633-45.

Horm Behav. 2009 May;55(5):633-45. doi: 10.1016/j.yhbeh.2009.03.015.

Effects of prenatal androgens on rhesus monkeys: a model system to explore the organizational hypothesis in primates.

Thornton J, Zehr JL, Loose MD.

Author information

Abstract

After proposing the organizational hypothesis from research in prenatally androgenized guinea pigs (Phoenix, C.H., Goy, R.W., Gerall, A.A., Young, W.C., 1959. Organizational action of prenatally administered testosterone propionate on the tissues mediating mating behavior in the female guinea pig. Endocrinology 65, 369-382.), the same authors almost immediately extended the hypothesis to a nonhuman primate model, the rhesus monkey. Studies over the last 50 years have verified that prenatal androgens have permanent effects in rhesus monkeys on the neural circuits that underlie sexually dimorphic behaviors. These behaviors include both sexual and social behaviors, all of which are also influenced by social experience. Many juvenile behaviors such as play, mounting, and vocal behaviors are masculinized and/or defeminized, and aspects of adult sexual behavior are both masculinized (e.g. approaches, sex contacts, and mounts) and defeminized (e.g. sexual solicits). Different behavioral endpoints have different periods of maximal susceptibility to the organizing actions of prenatal androgens. Aromatization is not important, as both testosterone and dihydrotestosterone are equally effective in rhesus monkeys. Although the full story of the effects of prenatal androgens on sexual and social behaviors in the rhesus monkey has not yet completely unfolded, much progress has been made. Amazingly, a large number of the inferences drawn from the original 1959 study have proved applicable to this nonhuman primate model.

More on brain androgenization . . . .

*". . . . The latest studies in 46, XX subjects exposed to prenatal androgens show that prenatal androgenization of 46,XX fetuses leads to marked masculinization of later gender-related behavior but does **not** lead to gender confusion/dysphoria. . . ."*

Gooren L. The biology of human psychosexual differentiation. Horm Behav. 2006 Nov;50(4):589-601.

Gooren L. The biology of human psychosexual differentiation. Horm Behav. 2006 Nov;50(4):589-601.

Most attempts to identify biological underpinnings of gender identity and sexual orientation in humans have investigated effects of sex steroids, so pivotal in the differentiation of the genitalia, showing strong parallels between animals and the human. The information on humans is derived from the so-called 'experiments of nature', clinical entities with a lesser-than-normal androgen exposure in XY subjects and a higher than normal androgen exposure in XX subjects. Prenatal androgenization appears to predispose to a male gender identity development, but apparently not decisively since 40-50% of 46,XY intersexed children with a history of prenatal androgen exposure do not develop a male gender identity. Obviously, male-to-female transsexuals, with a normal androgen exposure prenatally (there is no serious evidence to the contrary) develop a female gender identity, through unknown biological mechanisms apparently overriding the effects of prenatal androgens. The latest studies in 46, XX subjects exposed to prenatal androgens show that prenatal androgenization of 46,XX fetuses leads to marked masculinization of later gender-related behavior but does not lead to gender confusion/dysphoria. The example of female-to-male transsexuals, without evidence of prenatal androgen exposure, indicates that a male gender identity can develop without a significant androgen stimulus. So we are far away from any comprehensive understanding of hormonal imprinting on gender identity formation. Brain studies in homosexuals have not held up in replication studies or are in need of replication in transsexuals. Genetic studies and the fraternal birth order hypothesis provide indications of familial clustering of homosexuality but in many homosexuals these genetic patterns cannot be identified. The biological explanations advanced for the birth order hypothesis lack any experimental support.

What are the effects of testosterone at the time of male puberty?

- Development of secondary sex characteristics.

- Initiation of spermatogenesis.

- Initiation of libido, erections, ejaculation.

- Anabolism:
    - growth spurt
    - incr. muscle mass
    - incr. BMD
    - incr. [Hb]

- Acne.

What are the effects of “normal” adult male testosterone levels in men?

- **Maintenance of secondary sex characteristics.**

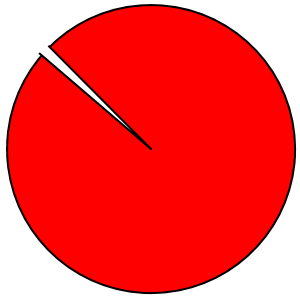
- **Maintenance of spermatogenesis.**

- **Libido, erections, ejaculation.**

In what forms does testosterone circulate in the body?

Free
2%

Biologically active



Bound
98%

Albumin - Loosely (weakly) bound **54%**

SHBG - Tightly bound* **44%**

Bioavailable T (BAT)

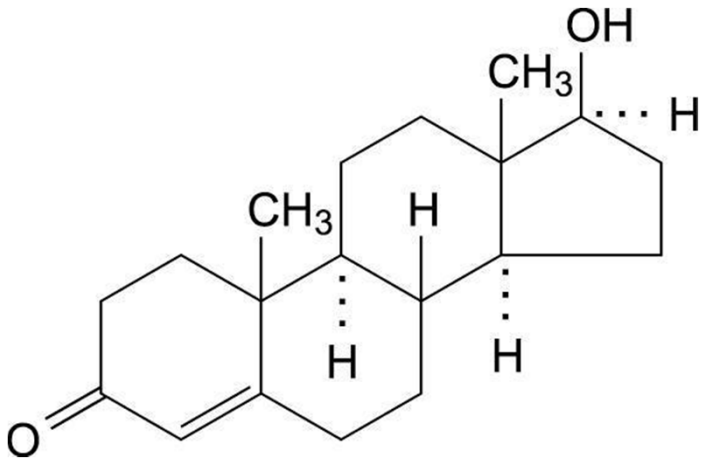
* Precipitable w/ ammonium sulfate ($T_{total} - T_{ASP} = BAT$)

Effect of androgens on SHBG: Decr. (-- > incr. free T)

ASP = ammonium sulfate precipitable testosterone; T distribution reference: Lepage R. Measurement of testosterone and its sub-fractions in Canada. Clin Biochem. 2006 Feb;39(2):97-108.

How should testosterone be measured?

Age group	Method
Adolescent males and adult men	Immunoassay is satisfactory
Children and women	Mass spectroscopy (need lower limits of detection)



How can free testosterone be determined?

Dialysis equilibrium **< --- definitive method (labor intensive)**

Ultrafiltration **< --- definitive method (labor intensive)**

Analog methods

Free androgen index

Calculated from total T & SHBG

Adv Clin Chem. 2014;63:59-84.
Free testosterone: clinical utility and important analytical aspects of measurement.
Shea JL, Wongt PY, Chen Y.
Abstract

Testosterone, the most abundant androgen in men, is a steroid hormone that is synthesized predominantly by the testes. In women, minor amounts are synthesized in the ovaries. Androgen precursors are also produced and secreted from the adrenal glands in both sexes, where they undergo peripheral conversion to testosterone. Circulating concentrations are approximately 15-25 times higher in adult men compared to women. Maintenance of these levels is necessary for development and maintenance of secondary sexual characteristics, libido, growth, prevention of osteoporosis, and most importantly in men, spermatogenesis. Most testosterone circulates tightly bound to sex hormone-binding globulin (SHBG) or weakly bound to albumin. A minor amount circulates as free testosterone, and it is believed that this is the metabolically active fraction. Measurement of free testosterone is important in the diagnosis of many diseases, most importantly disorders of androgen deficiency in men (i.e., hypogonadism) and androgen excess in women (i.e., polycystic ovary syndrome and hirsutism). Many methodologies are available for free testosterone measurement including the reference methods (equilibrium dialysis and ultrafiltration), analog immunoassay, and calculated free testosterone based on measurement of total testosterone, SHBG, and albumin. Moreover, measurement of bioavailable testosterone, a combination of albumin-bound and free testosterone, also has clinical utility and can be measured by selective protein precipitation or calculation. In this review, the advantages and limitations of each of these methods will be discussed in the context of clinical utility and implementation into a routine hospital laboratory. Furthermore, up and coming methodologies for free testosterone measurement, including liquid chromatography-tandem mass spectrometry, will also be discussed.

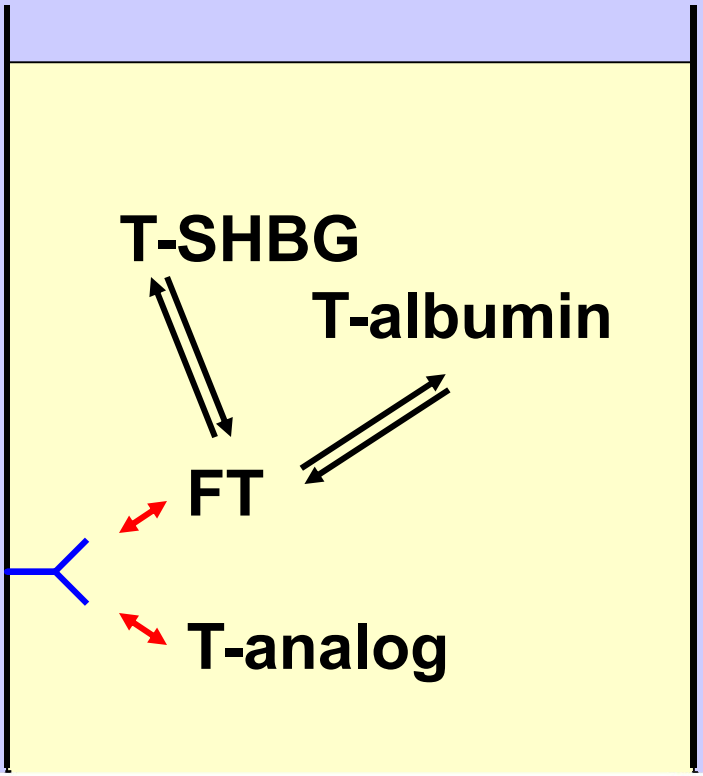
Can J Urol. 2012 Jun;19(3):6314-8.
A critical appraisal of accuracy and cost of laboratory methodologies for the diagnosis of hypogonadism: the role of free testosterone assays.

Morales A1, Collier CP, Clark AF.
Author information

Abstract

The biochemical diagnosis of male hypogonadism remains a controversial issue. The problem is compounded by the variety of laboratory assays available to measure serum testosterone (T) and the limited understanding, among clinicians, of their relative diagnostic validity. It is widely accepted that only the testosterone not bound to sex hormone-bounding globulin is metabolically active. Therefore, for diagnostic purposes it is frequent practice to order the measurement of free T (FT) or bioavailable T (BAT). Our objective is to describe the methods available for measuring FT and to review the literature to determine the relevance of ordering FT as a diagnostic laboratory tool in cases of suspected hypogonadism. We also provide our biochemical approach in evaluating men with T deficiency. The limited information available in this regard is frequently confined to the biochemistry literature. The few reliable studies indicate that analog-based measurement of FT offers no diagnostic or financial advantage over automated assay for total T. The manuscript also describes "How we do it." For optimal diagnostic accuracy and financial responsibility, total T and calculated FT (cFT) should be the tests employed for initial and confirmatory diagnosis respectively. Measurement of bioavailable T is an alternative option but not germane to the points to which we are calling attention in this paper. While clinicians should be discouraged from ordering FT assays, laboratories performing it should indicate what method was used and warned about possible reliability concerns. FT assays should no longer be a reimbursable test.

Analog methods



values for healthy men are almost 10 fold lower compared to reference FT methods, necessitating method specific reference intervals as well as prompting serious concern about the accuracy of the method. The premise of the assay is that the T analog does not interact with other proteins in the sample, a requirement that most commercial kits fail to fulfill.

Morales A, Collier CP, Clark AF. A critical appraisal of accuracy and cost of laboratory methodologies for the diagnosis of hypogonadism: the role of free testosterone assays. Can J Urol. 2012 Jun;19(3):6314-8.

What is the free androgen index?

$$\text{Ratio} = \frac{T}{SHBG}$$

Assessment: unreliable

Recommendation: do not use!

Morales A, Collier CP, Clark AF. A critical appraisal of accuracy and cost of laboratory methodologies for the diagnosis of hypogonadism: the role of free testosterone assays. Can J Urol. 2012 Jun;19(3):6314-8.

How can free testosterone "best" be determined in "routine" clinical laboratories?

Total T & SHBG (+/- albumin) --- > calculate free T

Concentration Testosterone = FT(free) + Alb-bound-T + [SHBG]-bound-T
Testosterone = [S] + $[S_A]$ + [SP]

Albumin

$\frac{[S_A]}{[S]}$ = constant = K_A x $C_{onc.}$Alb = $3.6x10^4$x 43g/l = $\frac{22.4}{69000}$

69000 =(molecular weight alb.)
K_A = = 3.6x104
for an average albumin conc. of 4.3 g/dL

or $[S_A]$ = 22.43 [S]

$[S] + [S_A] = (1 + 22.43)[S] = 23.43\ [S]$ (1)

SHBG

[P] = free SHBG

[SP] = steroid bound SHBG

$K = 10^9$ M
[S] +[P] « [SP] or $\frac{[S]}{[P]\ [K]}$ = [SP]

[P] + [SP] = [SHBG] or [P] = [SHBG] –[SP] (3)

Bioavailable
[Bio T] = [S] + $[S_A]$

Source: http://www.issam.ch/freetesuit.htm

"J Clin Endocrinol Metab 84:3666-3672, 1999 – A critical evaluation of simple methods for the estimation of free testosterone in serum"

Concentration Testosterone = FT(free) + Alb-bound-T + [SHBG]-bound-T

Testosterone = [S] + [S_A] + [SP]

· ***Albumin***

$\frac{[S_A]}{[S]}$ = constant = $K_A \times C_{conc.}Alb = 3.6\times10^4 \times \frac{43g/l}{69000} = \mathbf{22.4}$

69000 =(molecular weight alb.)

$K_A = 3.6\times10^4$

for an average albumin conc. of 4.3 g/dL

or **[S_A] = 22.43 [S]**

[S] + [S_A] = (1 + 22.43)[S] = **23.43 [S]** (1)

· ***SHBG***

[P] = free SHBG

[SP] = steroid bound SHBG

$K = 10^9$ M

[S] +[P] « [SP] or $[S] = \frac{[SP]}{[P]\,[K]}$ (2)

[P] + [SP] = [SHBG] **or [P] = [SHBG] –[SP]** (3)

· ***Bioavailable***

[Bio T] = [S] + [SA]

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http://www.issam.ch/freetesuit.htm

"J Clin Endocrinol Metab 84:3666-3672, 1999 – A critical evaluation of simple methods for the estimation of free testosterone in serum"

Example :

SHBG : 40 nmol/l = 40×10^{-9}

Testosterone = 288.4 ng/dl = **10×10^{-9} Mol = [SP] + 23.43 [S]**

$$[SP] = 10 \times 10^{-9} - 23.43\ [S]$$

From (3) $[P] = 40\ 10^{-9} - 10\ 10^{-9} + 23.43\ [S] = 30\ 10^{-9} + 23.43[S]$

From (2) and (1) $[S] = \frac{[SP]}{[K]\,[P]} = \frac{10\ 10^{-9} - 23.43\ [S]}{10^{9}\,(30\ 10^{-9} + 23.43[S])} = \frac{10\ 10^{-9} - 23.43\ [S]}{30 + 23.4\ 10^{9}[S]}$

$[S]\{ 30 + 23.43 \times 10^{9}\ [S]\} = 10\ 10^{-9} - 23.43[S]$

$30\ [S] + 23.43 \times 10^{9}\ [S]^2 + 23.43[S] - 10\ 10^{-9} = 0$

$23.43 \times 10^{9}\ [S]^2 + 53.43[S] - 10\ 10^{-9} = 0$ *second degree equation* $x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$

$a = 23.43 \times 10^{9}$

$b = 53.43$

$c = -\ 10\ 10^{-9}$

$$[S] = \frac{-53.43 + \sqrt{53.43^2 + 4 \times 23.43\ 10^{9} \times 10\ 10^{-9}}}{2 \times 23.43 \times 10^{9}} = \frac{-53.43 + \sqrt{2855+937}}{48.86\ 10^{9}} = \frac{-53.43+61.58}{48.86\ 10^{9}}$$

$[S] = 1.7388\ 10^{-10}$

$$[S]\ \% = \frac{1.7388^{-10} \times 100}{10\ 10^{-9}} = 1.74\ \%$$

$$FT = \frac{1.7388 \times 288.5}{100} = 5.02\ \text{ng/dl}$$

· ***Bioavailable***

Bio T = [S] + [SA] = [S] + 22.43 [S] (for the default albumin concentration of 4.3 g/dL)

http://www.issam.ch/freetesuit.htm

"J Clin Endocrinol Metab 84:3666-3672, 1999 – A critical evaluation of simple methods for the estimation of free testosterone in serum"

3.8. Salivary testosterone has also been shown to be a reliable substitute for free testosterone measurements but cannot be recommended for general use at this time, since the methodology has not been standardized and adult male ranges are not available in most hospital or reference laboratories (45) (Level 3, Grade B).

Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morales A, Morley JE, Schulman C, Thompson IM, Weidner W, Wu FC. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. Eur J Endocrinol. 2008 Nov;159(5):507-14.

When should testosterone be measured during the day?

Age	PM (1600) versus AM (0800)T
30-40 y/o	20-25% lower
70 y/o	10% lower

2008 Guidelines: 7 AM – 11 AM

What are the reference intervals for testosterone?

Developmental Stage	Testosterone (ng/dL)
I	<3
II	<3-432
III	65-778
IV	180-763
V	188-882
Adult male >19 y	348-1197

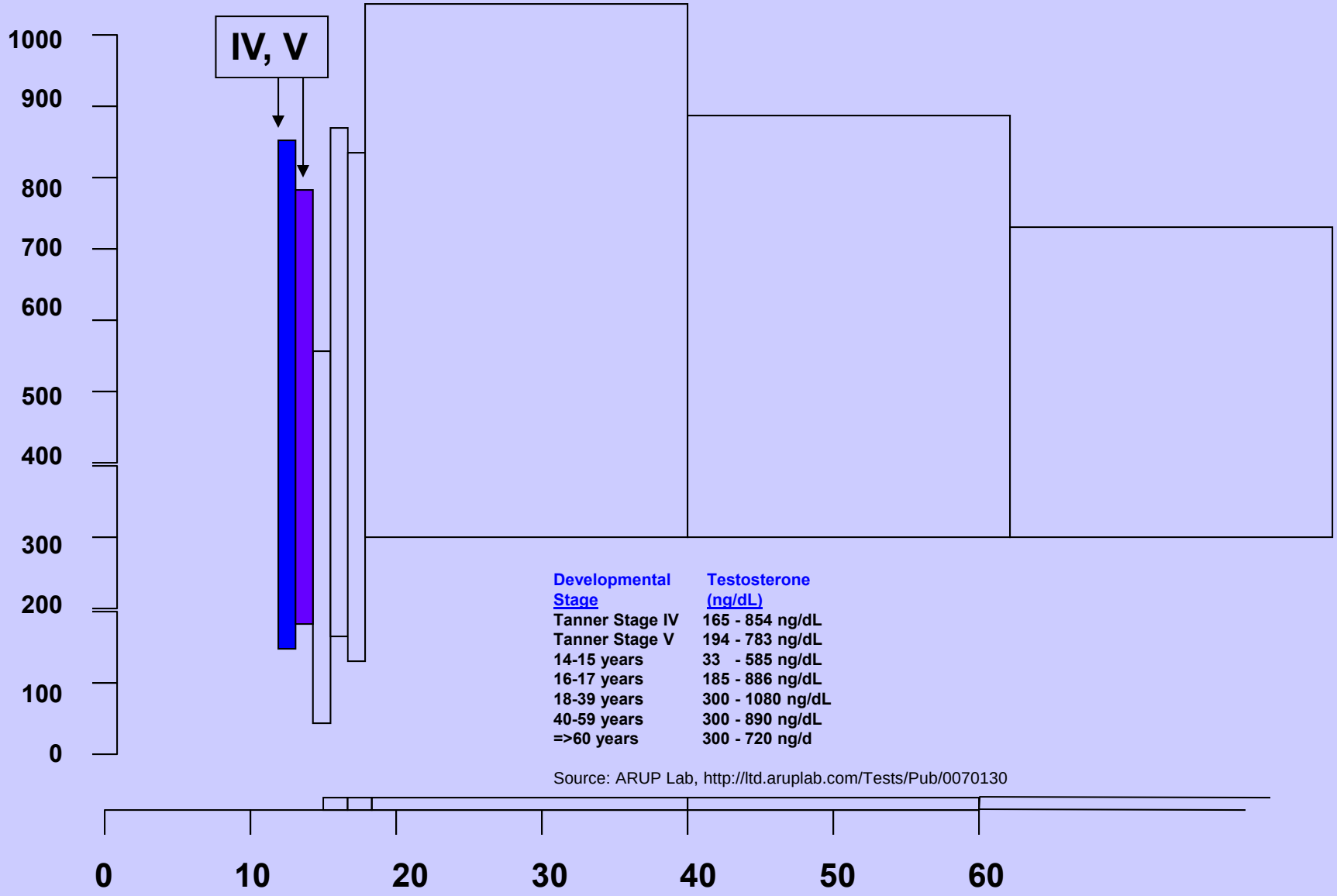
Source: Lab Corp

What are the reference intervals for testosterone?

Developmental Stage	Testosterone (ng/dL)		
Tanner Stage IV	165	-	854 ng/dL
Tanner Stage V	194	-	783 ng/dL
14-15 years	33	-	585 ng/dL
16-17 years	185	-	886 ng/dL
18-39 years	300	-	1080 ng/dL
40-59 years	300	-	890 ng/dL
=>60 years	300	-	720 ng/d

Source: ARUP Lab, http://ltd.aruplab.com/Tests/Pub/0070130

What are the reference intervals for testosterone?



Developmental Stage	Testosterone (ng/dL)
Tanner Stage IV	165 - 854 ng/dL
Tanner Stage V	194 - 783 ng/dL
14-15 years	33 - 585 ng/dL
16-17 years	185 - 886 ng/dL
18-39 years	300 - 1080 ng/dL
40-59 years	300 - 890 ng/dL
=>60 years	300 - 720 ng/d

Source: ARUP Lab, http://ltd.aruplab.com/Tests/Pub/0070130

1143 Japanese men 20-77 y/o

	Twenties	Thirties	Forties	Fifties	Sixties	Seventies	All ages
n	294	287	235	169	120	38	*1,143*
Xbar + 2SD	8.36	7.16	7.31	6.74	6.61	6.46	*7.50*
Xbar	4.98	4.30	4.20	3.91	3.83	3.84	*4.32*
Xbar - 2SD	2.47	2.17	1.95	1.84	1.80	1.90	*2.01*

(ng/mL)

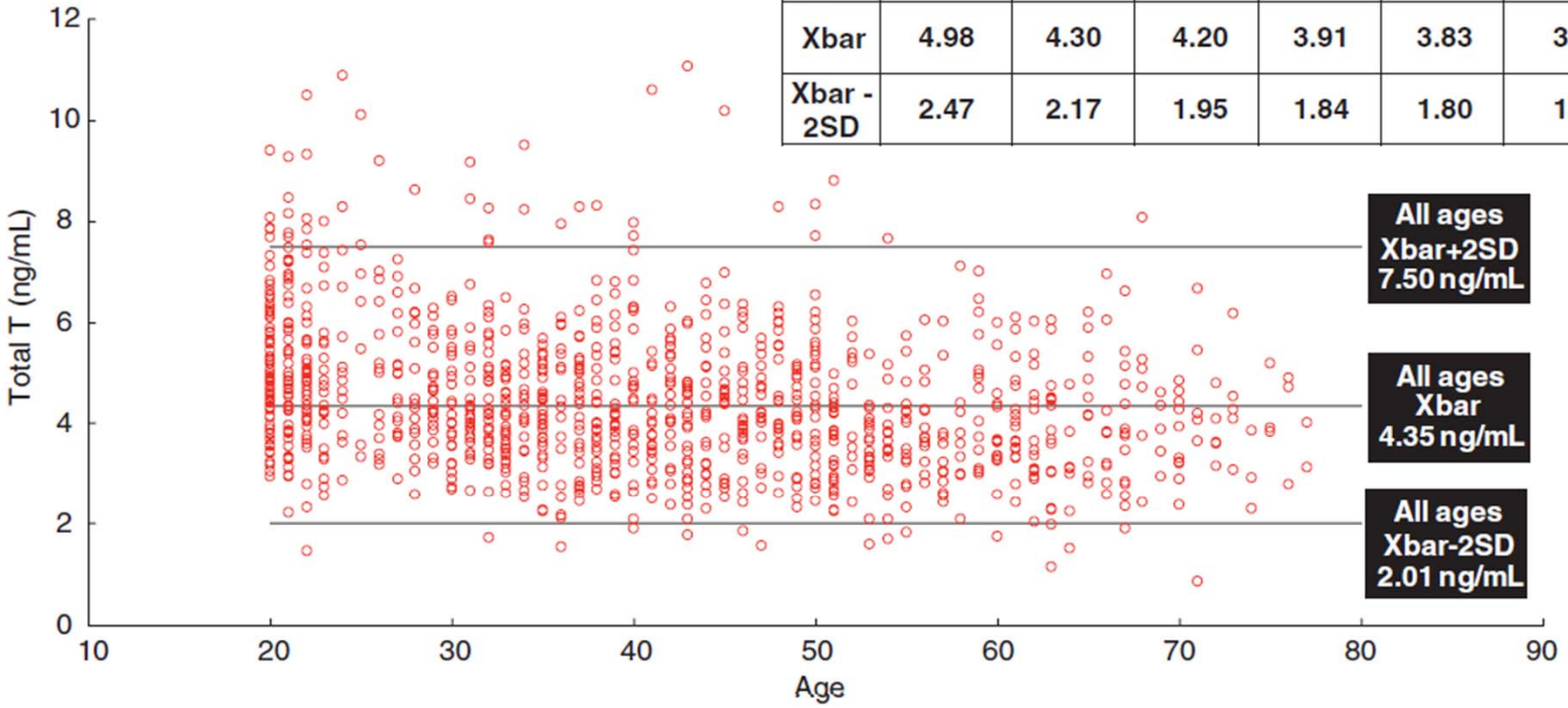


Fig. 1 For total testosterone, statistical analysis was performed on the data from all subjects aged 20 to 77 years, and the standard range was defined as Xbar ± 2SD. The upper limit (Xbar + 2SD) and lower limit (Xbar – 2SD) were 7.50 ng/mL and 2.01 ng/mL, respectively, with a mean (Xbar) of 4.35 ng/mL.

"The mean total T by age range decreases only to 80% of the young adult mean even during presenile and senile periods, when LOH occurs most frequently."

International Journal of Urology (2009) 16, 168–174; LOH = late-onset hypogonadism

1143 Japanese men 20-77 y/o

	Twenties	Thirties	Forties	Fifties	Sixties	Seventies
n	294	287	235	169	120	38
Xbar + 2SD	27.9	23.1	21.6	18.4	16.7	13.8
Xbar	16.8	14.3	13.7	12.0	10.3	8.5
Xbar - 2SD	8.5	7.6	7.7	6.9	5.4	4.5

(pg/mL)

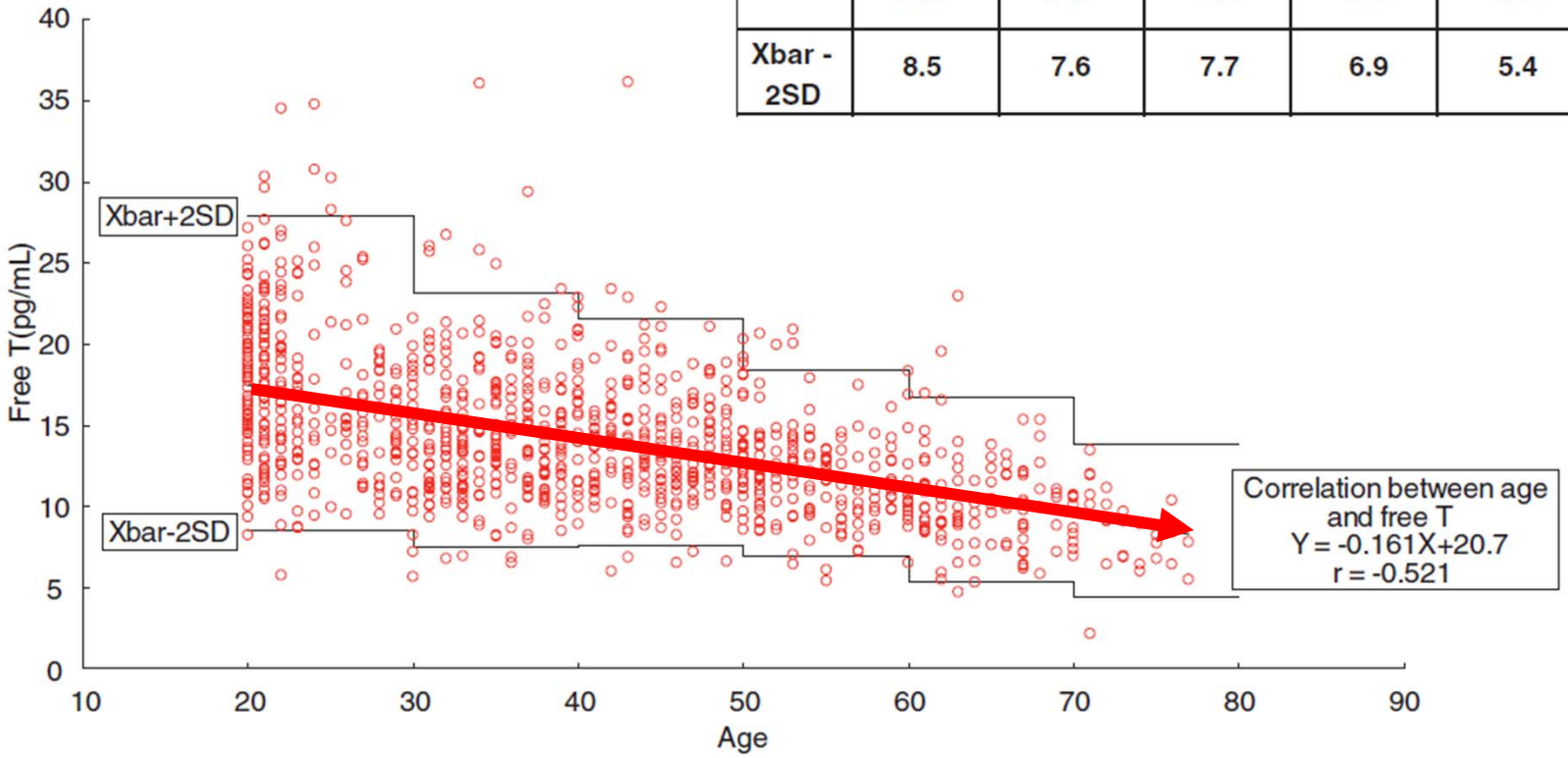


Fig. 2 For the analysis of free testosterone, all subjects aged 20 to 77 years were divided into age groups defined by 10-year intervals, and statistical analysis was conducted on data by age group. The standard range for each age group was defined as Xbar ± 2 standard deviation. A tendency toward gradual decrease

". . .free T level shows a linear decrease with aging and drops to 50% of the young adult mean."

International Journal of Urology (2009) 16, 168–174

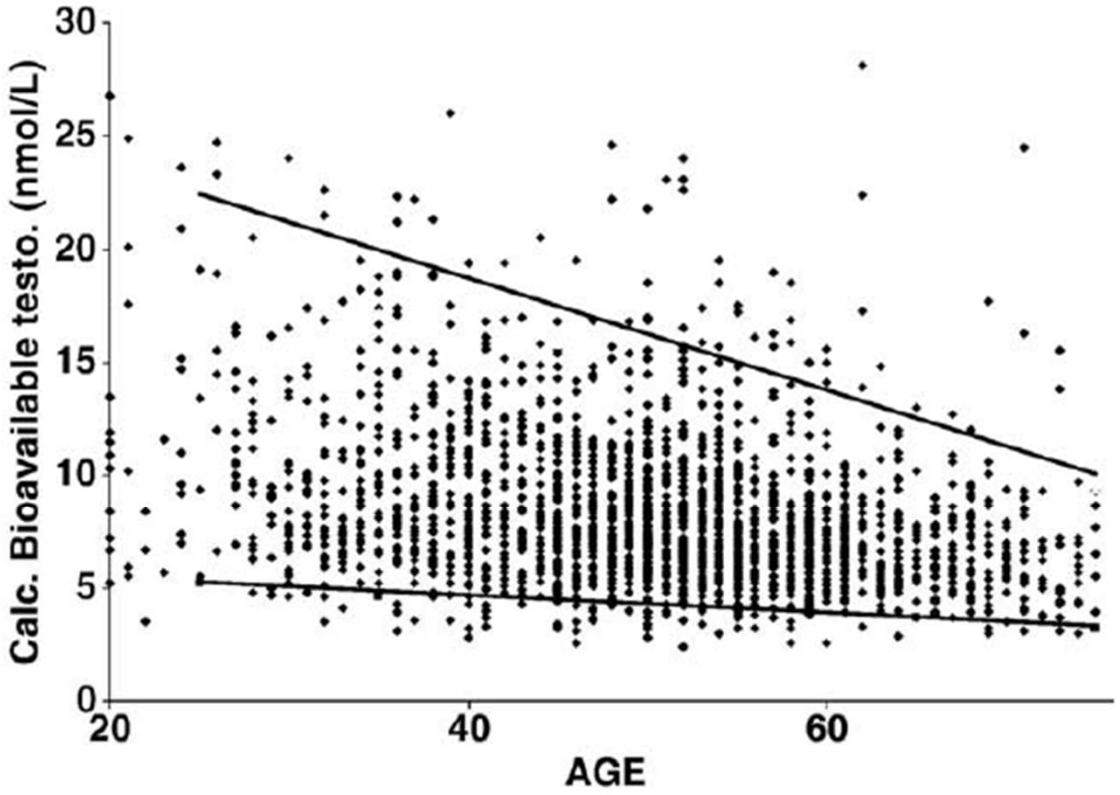


Fig. 8. Variation of calculated bioavailable testosterone vs. age in 3955 unscreened ambulatory male subjects. Solid lines represent the 5th and 95th percentile for different age groups. Samples were analyzed in the author's laboratory.

Lepage R. Measurement of testosterone and its sub-fractions in Canada. Clin Biochem. 2006 Feb;39(2):97-108.

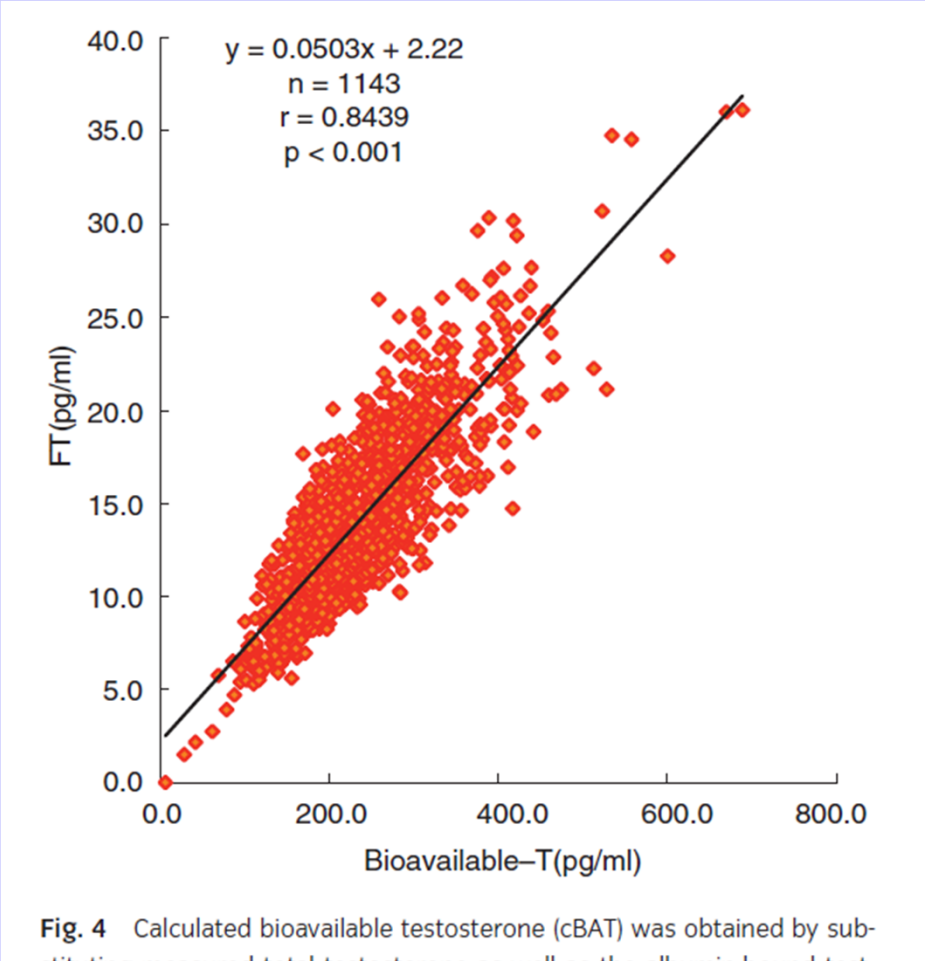


Fig. 4 Calculated bioavailable testosterone (cBAT) was obtained by sub-

The finding of a favorable correlation between BAT and free testosterone means that free testosterone can be used as an indicator to predict BAT levels.

International Journal of Urology (2009) 16, 168–174; BAT = bioavailable testosterone

Critical issues in measuring testosterone & FT

1. Reference intervals among laboratories should NOT be interchanged (need lab-specific ref intervals).

2. There is uncertainty in all methods & measurements.

3. There is intra-individual variation.

4. For repeated measurements, use the same lab.

5. Measure in the AM (and the ~same time w/ every repeated measurement).

6. Low T dx (T & SHBG) requires confirmation: 2 samples 2 wks apart w/ CV_i <20% (CV_i =>20% - repeat again).

What are the *symptoms* of late-onset hypogonadism? (i)

LOH is a syndrome characterized primarily by:

(1)The easily recognized features of diminished sexual desire (libido) and erectile quality and frequency, particularly nocturnal erections,

(2) Changes in mood with concomitant decreases in intellectual activity, cognitive functions, spatial orientation ability, fatigue, depressed mood and irritability,

(3) Sleep disturbances,

(4) Decrease in lean body mass with associated diminution in muscle volume and strength,

Source: Nieschlag E, Swerdloff R, Behre HM, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morley JE, Schulman C, Wang C, Weidner W, Wu FC. Investigation, treatment and monitoring of late-onset hypogonadism in males ISA, ISSAM, and EAU recommendations. European Urology. 2005;48:1–4.

What are the *symptoms* of late-onset hypogonadism? (ii)

(5) Increase in visceral fat,

(6) Decrease in body hair and skin alterations,

(7) Decreased bone mineral density resulting in osteopenia, osteoporosis and increased risk of bone fractures.

Source: Nieschlag E, Swerdloff R, Behre HM, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morley JE, Schulman C, Wang C, Weidner W, Wu FC. Investigation, treatment and monitoring of late-onset hypogonadism in males ISA, ISSAM, and EAU recommendations. European Urology. 2005;48:1–4.

What is the *definition* of late-onset hypogonadism?

Many definitions:

LOH is defined as a total testosterone level <300 ng/dL *combined with* the presence of three sexual symptoms:

- **Decreased frequency of morning erections**
- **Erectile dysfunction**
- **Decreased frequency of sexual thoughts**

Source: Rivas AM, Mulkey Z, Lado-Abeal J, Yarbrough S. Diagnosing and managing low serum testosterone. Proc (Bayl Univ Med Cent). 2014 Oct;27(4):321-4.

What causes LOH?

Primary hypogonadism:

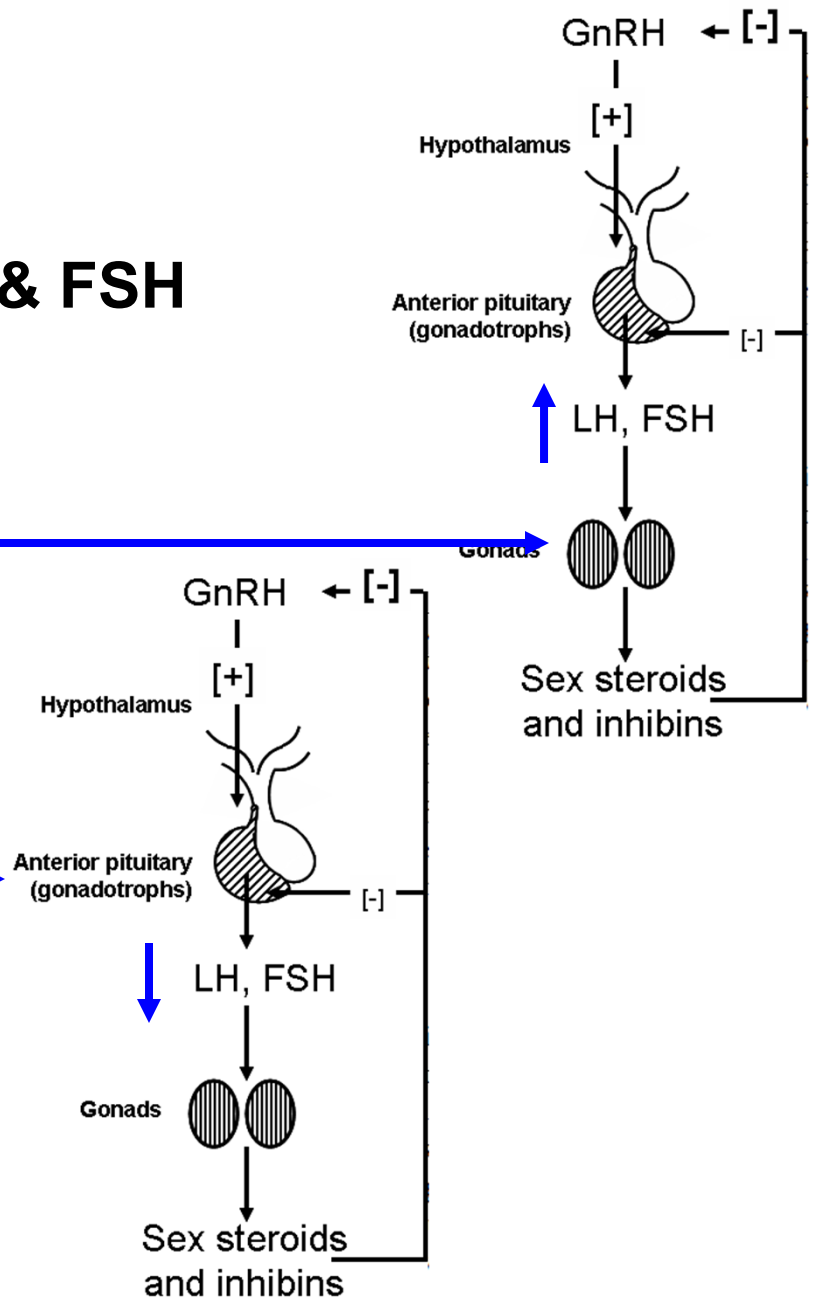
- Testicular failure: Incr. LH & FSH

Causes: LOH
47,XXY

Secondary hypogonadism:

- Decr. LH & FSH

R/O CNS disease



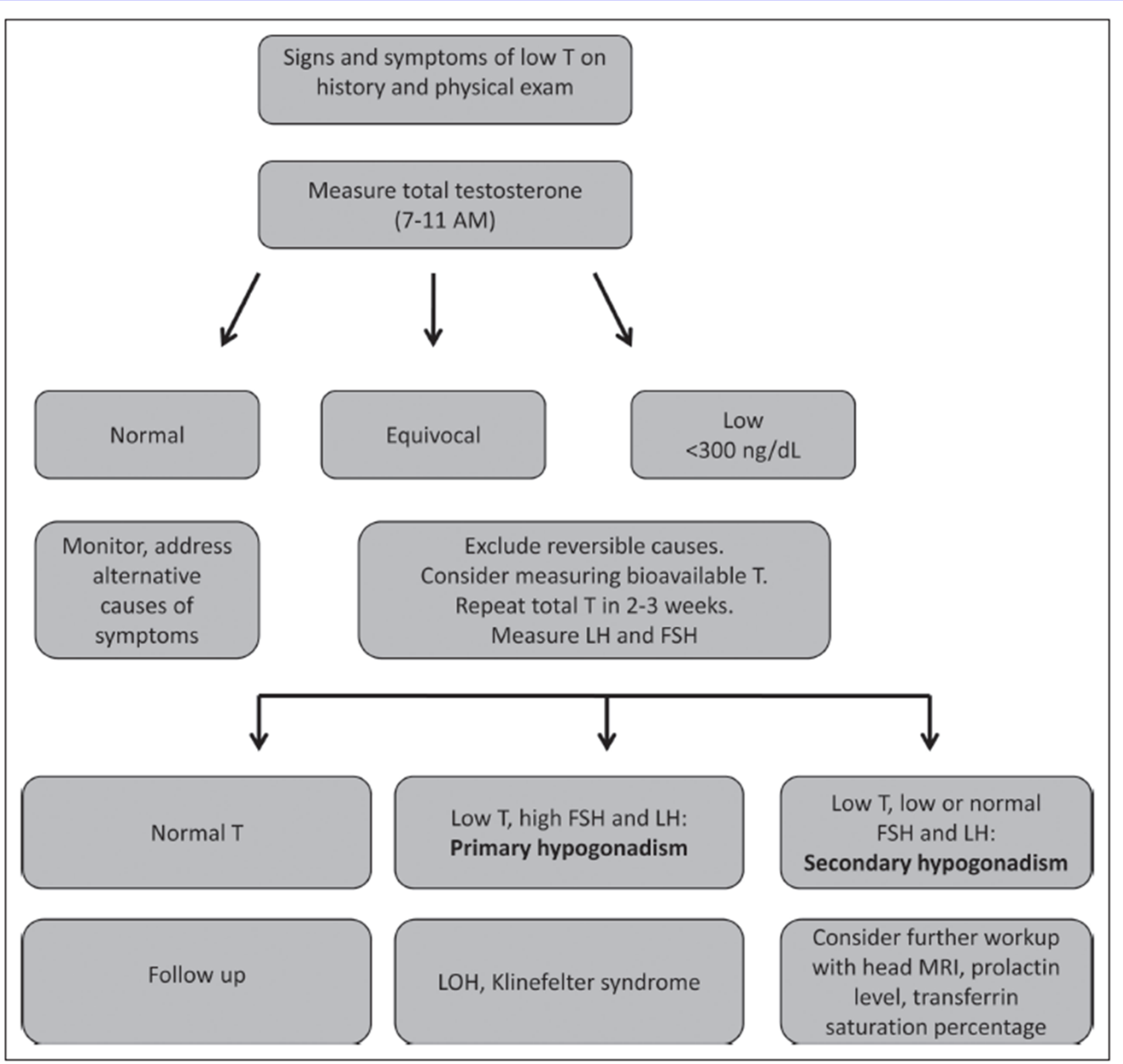


Figure 1. Diagnostic approach for patients suspected of having hypogonadism.

Source: Rivas AM, Mulkey Z, Lado-Abeal J, Yarbrough S. Diagnosing and managing low serum testosterone. Proc (Bayl Univ Med Cent). 2014 Oct;27(4):321-4.

Does male menopause (manopause, male climacteric, late-onset hypogonadism) actually occur?

FACT: Total and free T decline w/ incr. age

Symptoms of hypogonadism:
~ lack specificity & can be accounted for by other co-morbidities: chronic illness, depression, etc.

It is likely that LOH does really occur (as does "normal" aging)

Diagnosis of LOH:

Symptoms (+) low total T

if total T: "WNL" --- > measure free T

How common is late-onset hypogonadism?

"The actual prevalence of hypogonadism has been estimated to be 39% in men aged 45 years or older presenting to primary care offices in the United States."

Source: Rivas AM, Mulkey Z, Lado-Abeal J, Yarbrough S. Diagnosing and managing low serum testosterone. Proc (Bayl Univ Med Cent). 2014 Oct;27(4):321-4.

Massachusetts Male Aging Study:

Total T: <400 ng/dL (+) 3 signs/symptoms of low T:
Prevalence of 6% to 12%.

Source: O'Donnell AB, Araujo AB, McKinlay JB. The health of normally aging men: The Massachusetts Male Aging Study (1987–2004). Exp Gerontol 2004;39(7):975–984.

Best Pract Res Clin Endocrinol Metab. 2015 Jan;29(1):77-90. doi: 10.1016/j.beem.2014.09.008. Epub 2014 Oct 2.
Current topics in testosterone replacement of hypogonadal men.
Nieschlag E.
Author information
Abstract

All forms of hypogonadism - primary, secondary and late-onset - require testosterone substitution. The indication is given when the patient presents with symptoms of androgen deficiency and the serum testosterone levels are below normal. Several testosterone preparations and modes of application are available of which those producing physiologic serum levels should be preferred e.g. preferentially transdermal gels and long-acting intramuscular testosterone undecanoate. Testosterone substitution must be monitored at regular intervals, best at 3, 6 and 12 months after initiation and then annually. Parameters for surveillance include well-being, libido and sexual activity, measurement of serum testosterone levels, haemoglobin and haematocrit, PSA and digital rectal examination, and, biannually, bone mineral density. Testosterone has positive effects on comorbidities such as obesity, metabolic syndrome, diabetes type II, cardiovascular diseases and osteoporosis.

When should testosterone replacement be considered in "symptomatic" men?

Total T:

<230 mg/dL — **Tx'ed men usually benefit**

>350 mg/dL — **Tx not required**

230-350 mg/dL — **Measure free T or BAT**

(especially for obese men)

International Society of Andrology (ISA)
International Society for the Study of Aging Male (ISSAM)
European Association of Urology (EAU)
European Academy of Andrology (EAA)
American *Society* of Andrology (ASA)

Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morales A, Morley JE, Schulman C, Thompson IM, Weidner W, Wu FC. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. Eur J Endocrinol. 2008 Nov;159(5):507-14.

What are the economics of pharmacologic treatment of sexual dysfunction or androgen deficiency?

Worldwide revenue of Pfizer's Viagra from 2003 to 2013 (in million U.S. dollars)

The statistic shows the revenue of Pfizer's top product Viagra from 2003 to 2013. Pfizer Inc. is a multinational pharmaceutical corporation. The company is headquartered in Midtown Manhattan, New York City. In 2008, Pfizer's Viagra generated some 1.93 billion U.S. dollars of revenue.

Worldwide Viagra revenue

2013: $1.881 billion

Source:
Sign Up for Account
© Statista 2015

http://www.statista.com/statistics/264827/pfizers-worldwide-viagra-revenue-since-2003/

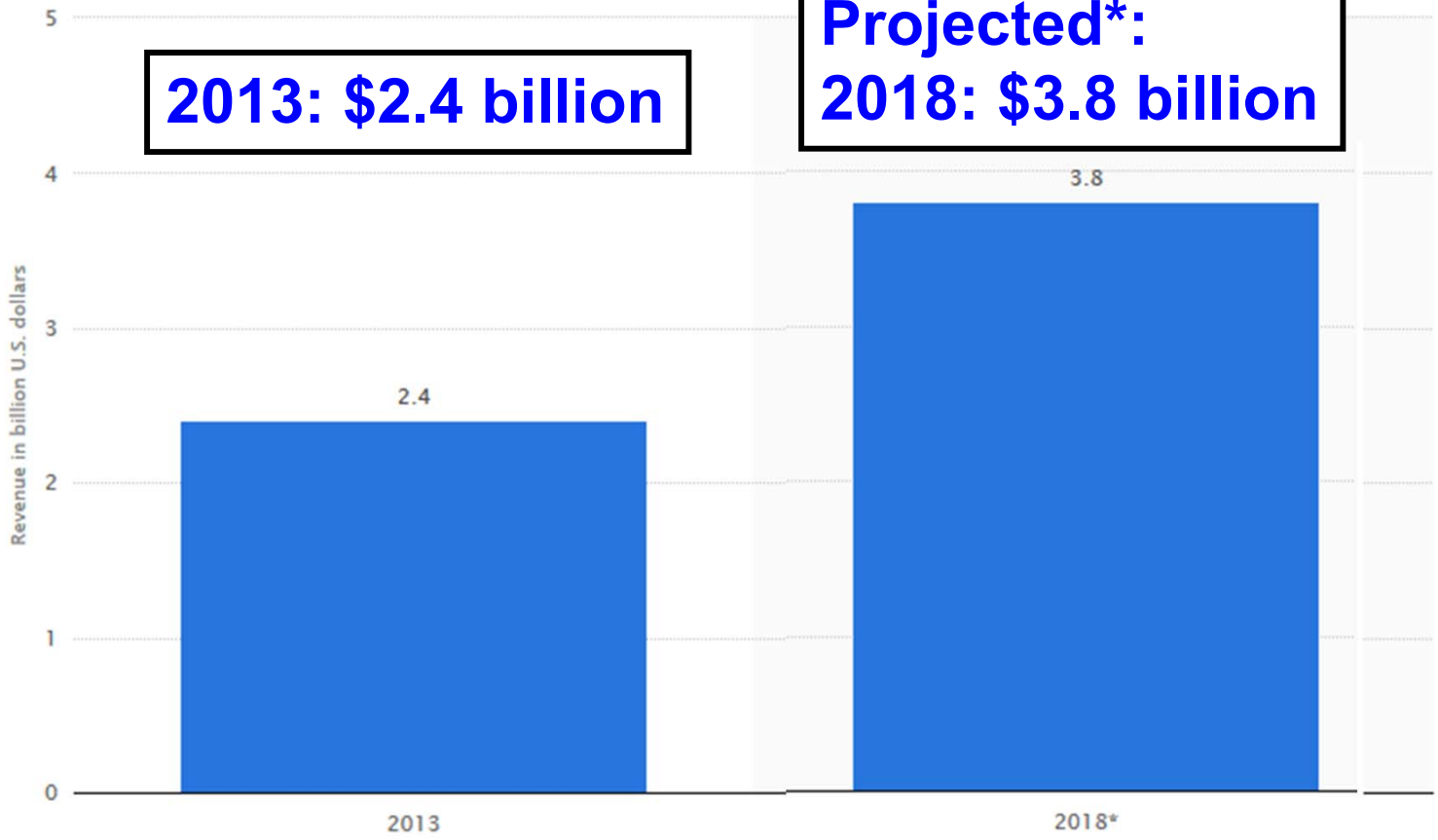
Annual testosterone drug revenue in the U.S. in 2013 and 2018 (in billion U.S. dollars)

This statistic depicts the annual testosterone drug revenue in the United States in 2013 and a projection for 2018, in billion U.S. dollars. In 2013, testosterone drugs generated a revenue of 2.4 billion U.S. dollars.

Annual testosterone revenue in U.S.

2013: $2.4 billion

Projected*:
2018: $3.8 billion



* Prior to March 3, 2015 FDA warning

Source:
Sign Up for Account

What is the "impact" on laboratory services for requests for testosterone measurements?

Study group: 321,674 18-85 y/o men; 2009 to 2012.

Result: 3.2% had a testosterone measurement for any reason!

	2009	2012	P	
Hz of testing:	2.5%	3.6%	<0.001	50% incr. in 3 yrs

Malik RD, Lapin B, Wang CE, Lakeman JC, Helfand BT. Are we testing appropriately for low testosterone?: characterization of tested men and compliance with current guidelines. J Sex Med. 2015 Jan;12(1):66-75.

1 in 5 men treated w/ T: "normal" T

- **Men treated by endocrinologists & urologists: more Hz'ly have a low T**

Baillargeon J, Urban RJ, Kuo YF, Holmes HM, Raji MA, Morgentaler A, Howrey BT, Lin YL, Ottenbacher KJ. Screening and monitoring in men prescribed testosterone therapy in the u.s., 2001-2010. Public Health Rep. 2015 Mar-Apr;130(2):143-52.

Who is most likely to be tested?

Caucasians

Incr. BMI

Presence of comorbid conditions, e.g., decr. libido, infertility, erectile dysfunction, osteoporosis, depression, prostate cancer, hypertension, chronic obstructive pulmonary disease and benign prostatic hyperplasia.

Malik RD, Lapin B, Wang CE, Lakeman JC, Helfand BT. Are we testing appropriately for low testosterone?: characterization of tested men and compliance with current guidelines. J Sex Med. 2015 Jan;12(1):66-75.

Baillargeon J, Urban RJ, Kuo YF, Holmes HM, Raji MA, Morgentaler A, Howrey BT, Lin YL, Ottenbacher KJ. Screening and monitoring in men prescribed testosterone therapy in the u.s., 2001-2010. Public Health Rep. 2015 Mar-Apr;130(2):143-52.

OBJECTIVES:

The Endocrine Society recommends testosterone therapy only in men with low serum testosterone levels, consistent symptoms of hypogonadism, and no signs of prostate cancer. We assessed screening and monitoring patterns in men receiving testosterone therapy in the U.S.
METHODS:

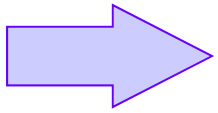
We conducted a retrospective cohort study of 61,474 men aged ≥40 years, and with data available in one of the nation's largest commercial insurance databases, who received at least one prescription for testosterone therapy from 2001 to 2010.
RESULTS:

In the 12 months before initiating treatment, 73.4% of male testosterone users received a serum testosterone test and 60.7% received a prostate-specific antigen (PSA) test. Among men who were tested, 19.5% did not meet Endocrine Society guidelines for low testosterone. In the 12 months after initiating treatment, 52.4% received a serum testosterone test and 43.3% received a PSA test. Multivariable analyses showed that those seen by either an endocrinologist or urologist were more likely to receive appropriate tests.
CONCLUSIONS:

A substantial number of men prescribed testosterone therapy did not receive testosterone or PSA testing before or after initiating treatment. In addition, almost one out of five treated men had baseline serum testosterone values above the threshold defined as normal by the Endocrine Society. Men treated by endocrinologists and urologists were more likely to have been treated according to guideline recommendations than men treated by other specialties, including primary care.

What are the risks of testosterone therapy?

Adverse androgen effects:

- Increased aggression/behavior changes
- Polycythemia
- Prostate enlargement
- Venous thrombo-embolism
- Dyslipidemia
- Hypertension
- AMI, stroke 

What are the risks of testosterone therapy?

FDA limits use of testosterone drugs, warns of risk

4 Hours Ago **3-3-2015**

REUTERS

The U.S. Food and Drug Administration has asked makers of prescription testosterone therapies to change their labeling to clarify that their products are approved only for men with specific medical conditions and could increase the risk of heart attacks and strokes.

Daniel Acker | Bloomberg | Getty Images

http://www.cnbc.com/id/102474330

FDA limits use of testosterone drugs, warns of risk
4 Hours AgoReuters

The U.S. Food and Drug Administration has asked makers of prescription testosterone therapies to change their labeling to clarify that their products are approved only for men with specific medical conditions and could increase the risk of heart attacks and strokes.

Prescriptions for low testosterone, or "Low T" have soared over the past decade, driven by a surge in use by men facing falling testosterone levels as they age.

Daniel Acker | Bloomberg | Getty Images

The number of men being prescribed testosterone jumped more than 75 percent, to 2.3 million, between 2009 and 2013. About 70 percent of these patients were between the ages of 40 and 64, the FDA said.

Tuesday's ruling restricts companies from marketing or promoting their products for age-related low testosterone.

The agency's announcement takes on board most of the recommendations of an independent advisory panel, which voted in September to endorse restricting the use of these treatments to men with medical conditions, such as genetic disorders or tumors, that impair testicular function.

The FDA has also asked manufacturers of approved products, including skin patches, solutions, intramuscular injections and topical gels, to conduct studies to determine whether the treatments raise cardiovascular risk.

Last year, the Canadian health regulator issued a similar warning of possible serious and life-threatening cardiovascular problems associated with these therapies.

AbbVie's AndroGel, one of the most widely used products, raked in sales of $934 million in 2014. Other products include Endo International's Testim and Eli Lilly & Co's Axiron.

A number of drugmakers, including Antares Pharma Inc, Repros Therapeutics Inc and Lipocine Inc, are currently developing their own low T treatments.

Last year, the agency mandated that manufacturers must include a warning about the risk of blood clots in the veins on their product labels.

Symptoms of low testosterone include loss of libido, decreased muscle mass, fatigue and depression.

Source: http://www.cnbc.com/id/102474330

What are the risks of testosterone therapy in older men?

FDA Warning: Testosterone Can Kill

Mar 03, 2015 | Gale Scott **3-3-2015**

Manufacturers of prescription testosterone products must change their drug labels to include a warning about increased risk of heart attacks and strokes.

The change, announced today by the US Food and Drug Administration (FDA) addresses the use of testosterone by men whose decreased level of the hormone is due to aging. The warning requirement could erode a multi-billion-dollar market for testosterone replacement products for men whose main concerns are more lifestyle than medical.

http://www.hcplive.com/product-news/FDA-Warning-Testosterone-Can-Kill?utm_source=Informz&utm_medium=HCPLive&utm_campaign=Trending%20News%203-3-15

Manufacturers of prescription testosterone products must change their drug labels to include a warning about increased risk of heart attacks and strokes.

The change, announced today by the US Food and Drug Administration (FDA) addresses the use of testosterone by men whose decreased level of the hormone is due to aging. The warning requirement could erode a multi-billion-dollar market for testosterone replacement products for men whose main concerns are more lifestyle than medical.

“Based on the available evidence from studies and expert input from an FDA advisory committee meeting [on Dec. 18, 2014] the FDA has concluded that there is a possible increased cardiovascular risk associated with testosterone use,” the FDA announcement said.

“These studies included aging men treated with testosterone” and some reports in those studied that found an increased risk of such events, including death.

Like estrogen replacement for menopausal women, testosterone therapy does reverse some effects of hormone loss due to aging, but carries health risks. The FDA announcement noted that testosterone is being widely prescribed as an anti-aging remedy for men.

Testosterone is FDA-approved only when low levels are due to “disorders of the testicles, pituitary gland, or brain that cause hypogonadism” and not “for no apparent reason other than aging.”

According to Medical Marketing & Media, among the more successful marketing campaigns is AbbVie’s “Low-T” campaign for AndroGel. The product had $1.37 billion in sales in the 12 months ending Oct. 31, 2013, making it the market leader.

Manufacturers offer testosterone replacement in gels, injections, implants and transdermal patches. –

See more at: http://www.hcplive.com/product-news/FDA-Warning-Testosterone-Can-Kill?utm_source=Informz&utm_medium=HCPLive&utm_campaign=Trending%20News%203-3-15#sthash.9V1pq6pl.dpuf

http://www.hcplive.com/product-news/FDA-Warning-Testosterone-Can-Kill?utm_source=Informz&utm_medium=HCPLive&utm_campaign=Trending%20News%203-3-15

FDA Drug Safety Communication: FDA evaluating risk of stroke, heart attack and death with FDA-approved testosterone products

Safety Announcement

[01-31-2014] The U.S. Food and Drug Administration (FDA) is investigating the risk of stroke, heart attack, and death in men taking FDA-approved testosterone products. We have been monitoring this risk and decided to reassess this safety issue based on the recent publication of two separate studies that each suggested an increased risk of cardiovascular events among groups of men prescribed testosterone therapy. We are providing this alert while we continue to evaluate the information from these studies and other available data, and will communicate our final conclusions and recommendations when the evaluation is complete.

At this time, FDA has not concluded that FDA-approved testosterone treatment increases the risk of stroke, heart attack, or death. Patients should not stop taking prescribed testosterone products without first discussing any questions or concerns with their health care professionals. Health care professionals should consider whether the benefits of FDA-approved testosterone treatment is likely to exceed the potential risks of treatment. The prescribing information in the drug labels of FDA-approved testosterone products should be followed.

Testosterone is a hormone essential to the development of male growth and masculine characteristics. Testosterone products are FDA-approved only for use in men who lack or have low testosterone levels in conjunction with an associated medical condition. Examples of these conditions include failure of the testicles to produce testosterone because of reasons such as genetic problems or chemotherapy. Other examples include problems with brain structures, called the hypothalamus and pituitary, that control the production of testosterone by the testicles.

None of the FDA-approved testosterone products are approved for use in men with low testosterone levels who lack an associated medical condition. FDA-approved testosterone formulations include the topical gel, transdermal patch, buccal system (applied to upper gum or inner cheek), and injection.

The first publication that prompted FDA to reassess the cardiovascular safety of testosterone therapy was an observational study of older men in the U.S. Veteran Affairs health system published in the Journal of the American Medical Association (JAMA) in November 2013.1 The men included in this study had low serum testosterone and were undergoing imaging of the blood vessels of the heart, called coronary angiography, to assess for coronary artery disease. Some of the men received testosterone treatment while others did not. On average, the men who entered the study were about 60 years old, and many had underlying cardiovascular disease. This study suggested a 30 percent increased risk of stroke, heart attack, and death in the group that had been prescribed testosterone therapy.

A second observational study reported an increased risk of heart attack in older men, as well as in younger men with pre-existing heart disease, who filled a prescription for testosterone therapy.2 The study reported a two-fold increase in the risk of heart attack among men aged 65 years and older in the first 90 days following the first prescription. Among younger men less than 65 years old with a pre-existing history of heart disease, the study reported a two- to three-fold increased risk of heart attack in the first 90 days following a first prescription. Younger men without a history of heart disease who filled a prescription for testosterone, however, did not have an increased risk of heart attack.

We urge health care professionals and patients to report side effects involving prescription testosterone products to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

http://www.fda.gov/drugs/drugsafety/ucm383904.htm

FDA adding general warning to testosterone products about potential for venous blood clots

[06/19/2014] The U.S. Food and Drug Administration (FDA) is requiring manufacturers to include a general warning in the drug labeling of all approved testosterone products about the risk of blood clots in the veins. Blood clots in the veins, also known as venous thromboembolism (VTE), include deep vein thrombosis (DVT) and pulmonary embolism (PE). The risk of venous blood clots is already included in the labeling of testosterone products as a possible consequence of polycythemia, an abnormal increase in the number of red blood cells that sometimes occurs with testosterone treatment. Because there have been postmarket reports of venous blood clots unrelated to polycythemia, FDA is requiring a change to drug labeling of all testosterone products to provide a more general warning regarding venous blood clots and to ensure this risk is described consistently in the labeling of all approved testosterone products.

Because these clots occur in the veins, this new warning is not related to FDA's ongoing evaluation of the possible risk of stroke, heart attack, and death in patients taking testosterone products. We are currently evaluating the potential risk of these cardiovascular events, which are related to blood clots in the arteries and are described in the Drug Safety Communication posted on January 31, 2014.

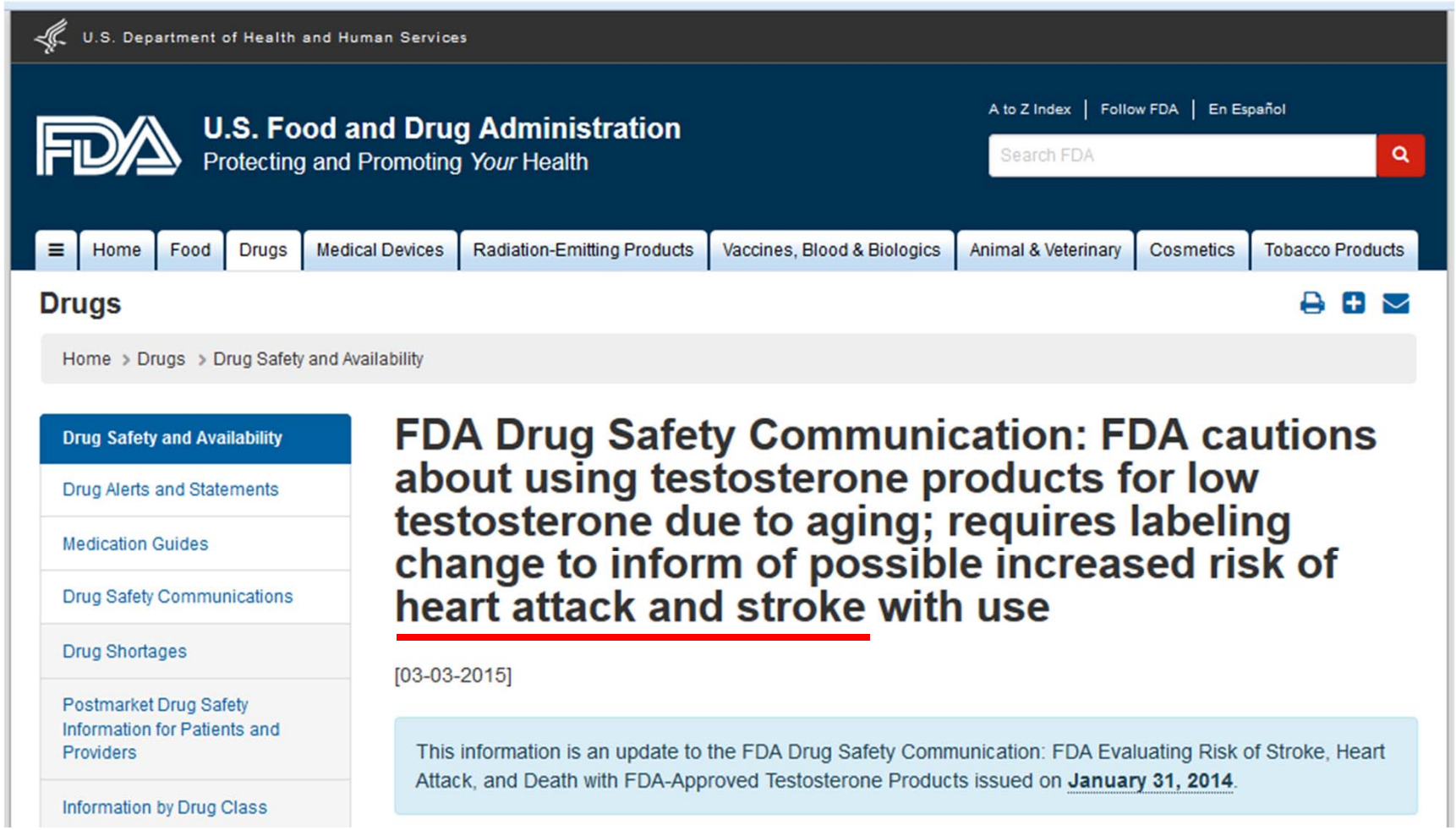
Testosterone products are FDA-approved for use in men who lack or have low testosterone levels in conjunction with an associated medical condition. Examples of these conditions include failure of the testicles to produce testosterone for reasons such as genetic problems or chemotherapy.

FDA asks health care professionals and consumers to report any adverse reactions to the FDA's MedWatch Safety Information and Adverse Event Reporting program:

- **Complete and submit the report online at https://www.accessdata.fda.gov/scripts/medwatch/**
- **Download and complete the form, then submit it via fax to 1-800-FDA-0178**

Source: http://www.fda.gov/Drugs/DrugSafety/ucm401746.htm

March 3, 2015 FDA warning!



Hazard ratios for MI, stroke and/or death: 0.61 – 2.30

http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm

A measure of how often a particular event happens in one group compared to how often it happens in another group, over time. In cancer research, hazard ratios are often used in clinical trials to measure survival at any point in time in a group of patients who have been given a specific treatment compared to a control group given another treatment or a placebo. A hazard ratio of one means that there is no difference in survival between the two groups. A hazard ratio of greater than one or less than one means that survival was better in one of the groups.

http://www.cancer.gov/dictionary?cdrid=618612

This information is an update to the FDA Drug Safety Communication: FDA Evaluating Risk of Stroke, Heart Attack, and Death with FDA-Approved Testosterone Products issued on January 31, 2014.

Safety Announcement

The U.S. Food and Drug Administration (FDA) cautions that prescription testosterone products are approved only for men who have low testosterone levels caused by certain medical conditions. The benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man's symptoms seem related to low testosterone. We are requiring that the manufacturers of all approved prescription testosterone products change their labeling to clarify the approved uses of these medications. We are also requiring these manufacturers to add information to the labeling about a possible increased risk of heart attacks and strokes in patients taking testosterone. Health care professionals should prescribe testosterone therapy only for men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests.

Testosterone is FDA-approved as replacement therapy only for men who have low testosterone levels due to disorders of the testicles, pituitary gland, or brain that cause a condition called hypogonadism. Examples of these disorders include failure of the testicles to produce testosterone because of genetic problems, or damage from chemotherapy or infection. However, FDA has become aware that testosterone is being used extensively in attempts to relieve symptoms in men who have low testosterone for no apparent reason other than aging. The benefits and safety of this use have not been established.

In addition, based on the available evidence from published studies and expert input from an Advisory Committee meeting, FDA has concluded that there is a possible increased cardiovascular risk associated with testosterone use. These studies included aging men treated with testosterone. Some studies reported an increased risk of heart attack, stroke, or death associated with testosterone treatment, while others did not.

Based on our findings, we are requiring labeling changes for all prescription testosterone products to reflect the possible increased risk of heart attacks and strokes associated with testosterone use. Health care professionals should make patients aware of this possible risk when deciding whether to start or continue a patient on testosterone therapy. We are also requiring manufacturers of approved testosterone products to conduct a well-designed clinical trial to more clearly address the question of whether an increased risk of heart attack or stroke exists among users of these products. We are encouraging these manufacturers to work together on a clinical trial, but they are allowed to work separately if they so choose.

Patients using testosterone should seek medical attention immediately if symptoms of a heart attack or stroke are present, such as:

- **Chest pain**
- **Shortness of breath or trouble breathing**
- **Weakness in one part or one side of the body**
- **Slurred speech**

A list of FDA-approved testosterone products can be found by searching for "testosterone" at Drugs@FDA.

We urge health care professionals and patients to report side effects involving testosterone products to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm

FDA has approved testosterone products to replace testosterone in men who have low testosterone levels associated with certain medical conditions. Examples of these conditions include:

- **Failure of the testicles to produce testosterone because of genetic problems or because of damage from chemotherapy**
- **Problems with the pituitary gland or part of the brain called the hypothalamus that control the production of testosterone by the testicles**

FDA-approved testosterone formulations include gels, solution, skin patch, intramuscular injection, pellets implanted under the skin, and a buccal system applied to the upper gum or inner cheek.

Testosterone is a hormone essential for the growth and development of male sex organs and maintenance of secondary male characteristics, such as facial hair.

In the past 5 years, the use of testosterone replacement therapy has increased significantly, from 1.3 million patients in 2009 to 2.3 million patients in 2013 receiving a prescription for a testosterone product. Currently, approximately 70 percent of men who receive testosterone prescriptions through retail pharmacies are between 40 and 64 years old.1 The most common diagnostic code associated with testosterone therapy is the non-specific diagnosis of "testicular hypofunction, not elsewhere classified."2

A diagnosis of hypogonadism requires laboratory evidence of low testosterone levels measured on at least two separate mornings. However, in one health plan database, approximately 20 percent of men who received testosterone prescriptions had no insurance claims for laboratory testing of testosterone levels.3

A list of FDA-approved testosterone products can be found by searching for "testosterone" at Drugs@FDA.

http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm

More Info for Patients

Testosterone replacement therapy is only approved for men who have low levels of testosterone related to certain medical conditions. Examples of these conditions include genetic problems, and chemotherapy or infections that have damaged the testicles.

The benefit and safety of testosterone have not been established in men who have low testosterone levels for no reason other than age, even if symptoms seem related to low testosterone. Testosterone levels can decrease naturally as men age, and sometimes these levels can become lower than the normal range seen in young, healthy men. Aging men can also experience signs and symptoms such as decreases in energy level and problems with sexual function, but it is uncertain whether these are caused by the lowered testosterone levels or due to normal aging. Therefore, the need to replace testosterone in these aging men is unclear.

Heart attacks and strokes have been reported with testosterone treatment. Seek medical attention right away if you have symptoms of a heart attack or stroke, such as:

- **Chest pain**
- **Shortness of breath or trouble breathing**
- **Weakness in one part or one side of the body**
- **Slurred speech**

Read the patient Medication Guide or patient information leaflet you get along with your prescription testosterone product. These materials explain the benefits and risks associated with testosterone use.

Talk to your health care professional if you have questions or concerns about testosterone treatment.

A list of FDA-approved testosterone products can be found by searching for "testosterone" at Drugs@FDA.

Report side effects from testosterone treatment to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

More Info for Health Care Professionals

Testosterone replacement therapy is approved for use only in men with primary or secondary hypogonadism resulting from certain medical conditions.

The safety and efficacy of testosterone replacement therapy for age-related hypogonadism have not been established.

Before initiating testosterone replacement therapy, ensure that the diagnosis of hypogonadism has been confirmed with laboratory testing. Verify that serum testosterone concentrations have been measured on at least two separate mornings and are consistently below the normal range. Avoid measuring testosterone concentrations later in the day, when measurements can be low even in men who do not have hypogonadism.

For each patient, weigh the potential increased risk of major adverse cardiovascular outcomes and other risks of testosterone replacement therapy against the potential benefits of treating hypogonadism.

Inform patients of the potential increased cardiovascular risk associated with testosterone replacement therapy.

Encourage patients to read the patient Medication Guide or patient information leaflet they receive with their testosterone prescriptions.

Report adverse events involving testosterone treatment to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.
http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm

http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm

Data Summary

FDA reviewed five observational studies4-8 and two meta-analyses of placebo-controlled trials9,10 to examine the risk of cardiovascular events associated with testosterone replacement therapy (TRT). The five observational studies were retrospective cohort studies that reported conflicting results. Two of these studies found statistically significant cardiovascular harm with TRT (Vigen and Finkle), 4-5 two studies found a statistically significant mortality benefit with TRT (Shores and Muraleedharan), 6-7 and one study was inconclusive (Baillargeon).8

The Vigen study evaluated male veterans who underwent angiography and had low testosterone concentrations. On average, testosterone-treated men were 64 years old and untreated men were 61 years old. This study found an increased risk with TRT compared to no TRT for the composite cardiovascular outcome of myocardial infarction, stroke, and death (Hazard Ratio [HR]=1.29, 95% Confidence Interval [CI]: 1.04-1.58).4

The Finkle study evaluated TRT users in a large claims database. The men included in this study were on average 54 years old. This study found an increased risk of non-fatal myocardial infarction during the 90 days following an initial prescription for TRT compared to the pre-TRT period (Relative Risk [RR]=1.36, 95% CI: 1.03-1.81).5

The Shores study evaluated a population of male veterans older than 40 years of age with low testosterone and found a decreased risk of all-cause mortality with TRT compared to no TRT (HR=0.61, 95% CI: 0.42-0.88).6

The Muraleedharan study evaluated men with type 2 diabetes in the United Kingdom. The main analysis assessed mortality in men with low serum testosterone concentrations compared to men with normal serum testosterone concentrations. Mortality was also assessed in a subgroup analysis of treated and untreated men with low serum testosterone; an increased risk of all-cause mortality in men with no TRT compared to those on TRT was found (HR=2.30, 95% CI: 1.30-3.90).7

Finally, the Baillargeon study evaluated men older than 65 years of age enrolled in Medicare and found no overall increase in risk of hospitalization for myocardial infarction when comparing those treated with TRT to those receiving no TRT (HR=0.84, 95% CI: 0.69-1.02).8

The Xu meta-analysis involved 27 published, randomized, placebo-controlled trials representing 2,994 mostly middle-aged and older male participants (1,773 treated with testosterone and 1,261 treated with placebo) who reported 180 cardiovascular-related adverse events.9 This study found that testosterone therapy was associated with an increased risk of adverse cardiovascular events (Odds Ratio [OR]=1.5, 95% CI: 1.1-2.1); however, methodological issues limit conclusions. These limitations include inconsistent and incomplete reporting of adverse events; substantial clinical heterogeneity in the design and conduct of the component trials and the types of cardiovascular outcomes included in the analyses; potential bias resulting from selection of component trials; and variable quality of the trials, particularly with regard to ascertainment of cardiovascular safety outcomes and balance in cardiovascular risk factors and discontinuation rates across study arms.

The Corona meta-analysis involved 26 published, randomized, controlled trials, 20 of which were also included in the Xu meta-analysis. The included studies represented 3,236 men (1,895 men treated with testosterone, 1,341 men treated with placebo) who reported 51 major adverse cardiovascular events, defined as cardiovascular death, non-fatal myocardial infarction or stroke, and serious acute coronary syndromes or heart failure.10 This study did not find a statistically significant increased risk of these cardiovascular events associated with testosterone treatment. Similar to the first meta-analysis, this study had methodological issues that limit conclusions. These issues include incomplete adverse event reporting in the published trials, clinical trial heterogeneity, possible treatment arm imbalances in cardiac risk factors, high or unbalanced discontinuation rates in some component trials, and the potential for bias in trial selection and interpretation of reported adverse events.

The five observational studies and the Xu meta-analysis were discussed at a joint meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee on September 17, 2014. Based on these findings, the advisory committee members were in general agreement that the signal of cardiovascular risk is weak and that only a prospective, well-controlled clinical trial could determine whether testosterone causes cardiovascular harm. The Corona study was recently published and could not be reviewed in time to be presented at the Advisory Committee meeting; however, we have reviewed the study and factored its findings into our overall assessment.

For complete reviews, background information, and minutes of the September 17, 2014, Advisory Committee meeting, click here.

http://www.fda.gov/Drugs/DrugSafety/ucm436259.htm

Symphony Health Solutions Anonymous Patient Longitudinal Database®. Years 2010-2013. Accessed May 2014.

Encuity Research, LLC Treatment Answers™. Years 2009-2013. Accessed May 2014.

IMS Lifelink Health Plan claims Database. Reporting years 2008-2013. Accessed June 2014.

Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013;310:1829-36.

Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One 2014;9:e85805.

Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. J Clin Endocrinol Metab 2012;97:2050-8.

Muraleedharan V, Marsh H, Kapoor D, Channer KS, Jones TH. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol 2013;169:725-33.

Baillargeon J, Urban RJ, Kuo YF et al. Risk of myocardial infarction in older men receiving testosterone therapy. Ann Pharmacother 2014.

Xu L, Freeman G, Cowling BJ, Schooling CM (2013). Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med, 11, 108. Additional files can be accessed online at http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3648456/.

Corona G, Maseroli E, Rastrelli G, Isidori AM, Sforza A, Mannucci E et al. (2014). Cardiovascular risk associated with testosterone-boosting medications: a systematic review and meta-analysis. Expert Opin Drug Saf, 13, 1327-1351.

SAN DIEGO, CA — Two new studies muddy the waters on the potential cardiovascular risks previously linked to testosterone-replacement therapy in men, with both studies suggesting the therapy might not be causing the cardiovascular harm suggested in previous analyses[1,2]. Both are scheduled for the presentation later this week at the American College of Cardiology (ACC) 2015 Scientific Sessions.

The first study included 7245 men with low testosterone levels from 15 hospitals and 150 clinics. Overall, the cardiovascular event rate—a composite of MI, stroke, or death—was 5.5% among those who received testosterone therapy and 6.7% among those who did not. After adjustment for baseline differences between the treated and untreated patients, the difference in the cardiovascular event rate was not statistically significant.

In the second study, a meta-analysis of 29 studies with more than 122 000 men, researchers found testosterone therapy was not associated with a significantly increased risk of adverse cardiovascular outcomes.

"When we pulled out all the studies so far, testosterone in any form—whether it was a gel, an injection, or older pills—did not increase the risk of cardiovascular events, such as heart attack, sudden cardiac death, stroke, or hospitalization for heart failure," Dr Pawan Patel (Regions Hospital, St Paul, MN), lead investigator of the meta-analysis, told heartwire . "Now, this is a not long-term, prospective, randomized controlled trial. Only with those long-term randomized controlled trials will we be able to say whether testosterone causes cardiovascular events .

http://www.medscape.com/viewarticle/841098?nlid=78305_2825&src=wnl_edit_medn_imed&uac=65959EZ&spon=18

How should testosterone-treated men be monitored?

Lab	Comment
Testosterone	"Monitoring"
Hb/Hct	Risk of polycythemia
Lipids	Risk of dyslipidemia
AST	Risk of hepatotoxicity
PSA	Concern regarding risk of prostate cancer
Semen analysis	If infertility is present: reduced sperm

Non-Lab	
BP	Salt retention, incr. BP
DRE	Concern regarding risk of prostate cancer
DexaScan	BMD should incr. w/ T tx

Best Pract Res Clin Endocrinol Metab. 2015 Jan;29(1):77-90. doi: 10.1016/j.beem.2014.09.008. Epub 2014 Oct 2.
Current topics in testosterone replacement of hypogonadal men.
Nieschlag E.
Author information
Abstract

All forms of hypogonadism - primary, secondary and late-onset - require testosterone substitution. The indication is given when the patient presents with symptoms of androgen deficiency and the serum testosterone levels are below normal. Several testosterone preparations and modes of application are available of which those producing physiologic serum levels should be preferred e.g. preferentially transdermal gels and long-acting intramuscular testosterone undecanoate. Testosterone substitution must be monitored at regular intervals, best at 3, 6 and 12 months after initiation and then annually. Parameters for surveillance include well-being, libido and sexual activity, measurement of serum testosterone levels, haemoglobin and haematocrit, PSA and digital rectal examination, and, biannually, bone mineral density. Testosterone has positive effects on comorbidities such as obesity, metabolic syndrome, diabetes type II, cardiovascular diseases and osteoporosis.

IMPORTANT INFORMATION ABOUT MONITORING

MONITORING AND FOLLOW-UP

10.3. Inadequate data are available to determine the optimal serum testosterone level for efficacy and safety. For the present time, mid to lower young adult male serum testosterone levels seem appropriate as the therapeutic goal (85). Sustained supraphysiological levels should be avoided. No evidence exists for or against the need to maintain the physiological circadian rhythm of serum testosterone levels (Level 3, Grade B).

Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morales A, Morley JE, Schulman C, Thompson IM, Weidner W, Wu FC. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. Eur J Endocrinol. 2008 Nov;159(5):507-14.

IMPORTANT INFORMATION ABOUT MONITORING

MONITORING AND FOLLOW-UP
The general target level for testosterone ranges from 350 to 750 ng/dL, which is roughly the range for healthy, androgen sufficient adult men. Testosterone levels should be monitored 3 to 6 months after initiation of treatment. Patients receiving the intramuscular testosterone enanthate or cypionate should have levels checked midway between injections, and levels should be checked 3 to 12 hours after application in the case of transdermal patches (11, 13).

The recommended duration of testosterone administration is uncertain. A hematocrit test is recommended prior to therapy initiation to establish a baseline for future monitoring. Hematocrit and prostate-specific antigen (PSA) levels should be measured 3 to 6 months after treatment initiation and then annually. TRT should be reconsidered in patients with a hematocrit >50%. An increase in PSA of more than 1.4 ng/mL within a 12-month period of testosterone treatment or an International Prostate Symptom Score above 19 should prompt urological evaluation. On the other hand, what should a clinician do with a PSA value that increases to a lesser degree per year but is steadily increasing every time it is checked? This can be managed using the concept of PSA velocity. Any PSA velocity >0.4 ng/mL per year should also prompt urological evaluation (at least 2 years of measurements are needed, based on PSA values measured at least 6 months after initiating therapy). For example, PSA levels of 1.5 ng/mL, 2.3 ng/mL, and 3.3 ng/mL over 3 years do not meet the fi rst indication for urology referral (more than 1.4 ng/mL over a year's time) but show an average PSA velocity of 0.9 ng/mL and require referral based on that criterion (11).

Source: Source: Rivas AM, Mulkey Z, Lado-Abeal J, Yarbrough S. Diagnosing and managing low serum testosterone. Proc (Bayl Univ Med Cent). 2014 Oct;27(4):321-4.

Am J Health Syst Pharm. 2015 Apr 1;72(7):536-41. doi: 10.2146/ajhp140128.
Recurrence of prostate cancer in patients receiving testosterone supplementation for hypogonadism.
Gray H1, Seltzer J2, Talbert RL1.
Author information
Abstract
PURPOSE:

The relationship between recurrent prostate cancer risk and testosterone replacement therapy (TRT) for hypogonadal men is explored.
SUMMARY:

The medical literature was searched to identify articles evaluating the use of TRT in symptomatic hypogonadal men with a history of prostate cancer. Eight English-language articles investigating TRT use in hypogonadal men with a history of prostate cancer were analyzed. For evaluative purposes, the normal ranges used for prostate-specific antigen (PSA) and total testosterone levels were less than 4.0 ng/mL and 300-1000 ng/dL, respectively. Most trials were small and involved patients with localized prostate cancer treated with radical prostatectomy or radiotherapy, though patients with metastatic disease or a Gleason score of ≥8 were included in a few studies. TRT was administered in a variety of dosages and dosage forms for up to nine years to manage hypogonadal symptoms. Testosterone concentrations increased, as expected, after TRT, but serum PSA levels remained below 0.1 ng/mL in the majority of patients. PSA levels were found to increase in select patients with high-risk and metastatic disease, but these elevations were not accompanied by disease progression. These studies have suggested a potential benefit for TRT use in select symptomatic hypogonadal men with a history of prostate cancer. Data were limited, however, by the retrospective nature of most studies, the lack of control groups, small sample sizes, and short follow-up periods.

CONCLUSION:

There is insufficient evidence to withhold TRT in certain populations of men with a history of prostate cancer.

Read this ---- >

Medicine (Baltimore). 2015 Jan;94(3):e410. doi: 10.1097/MD.0000000000000410.

The effect of testosterone replacement therapy on prostate-specific antigen (PSA) levels in men being treated for hypogonadism: a systematic review and meta-analysis.

Kang DY1, Li HJ.
Author information

Abstract

Testosterone replacement therapy is used for the treatment of age-related male hypogonadism, and prostate-specific antigen (PSA) is a primary screening tool for prostate cancer. The systematic review and meta-analysis aimed to determine the effect of testosterone replacement therapy on PSA levels.Medline, Cochrane Library, EMBASE, and Google Scholar databases were searched until February 28, 2014, and inclusion criteria were as follows: randomized controlled trial; intervention group received testosterone/androgen replacement therapy; control group did not receive treatment; and no history of prostate cancer. The primary outcome was change of PSA level between before and after treatment. Secondary outcomes were elevated PSA level after treatment, and the number of patients who developed prostate cancer.After initially identifying 511 articles, 15 studies with a total of 739 patients that received testosterone replacement and 385 controls were included. The duration of treatment ranged from 3 to 12 months. Patients treated with testosterone tended to have higher PSA levels, and thus a greater change than those that received control treatments (difference in means of PSA levels=0.154, 95% confidence interval [CI] 0.069 to 0.238, P<0.001). The difference in means of PSA levels were significant higher for patients that received testosterone intramuscularly (IM) than controls (difference in means of PSA levels=0.271, 95% CI 0.117-0.425, P=0.001). Elevated PSA levels after treatment were similar between patients that received treatment and controls (odds ratio [OR]=1.02, 95% CI 0.48-2.20, P=0.953). Only 3 studies provided data with respect to the development of prostate cancer, and rates were similar between those that received treatment and controls.Testosterone replacement therapy does not increase PSA levels in men being treated for hypogonadism, except when it is given IM and even the increase with IM administration is minimal.

Read this ---- >

Nat Rev Urol. 2014 Sep;11(9):526-30. doi: 10.1038/nrurol.2014.163. Epub 2014 Jul 29.
The safety of testosterone supplementation therapy in prostate cancer.
Dupree JM1, Langille GM1, Khera M1, Lipshultz LI1.
Author information
Abstract

Patients with prostate cancer can present with hypogonadism and experience health and quality-of-life declines related to low testosterone levels. Despite generations of urological dogma suggesting that testosterone supplementation therapy (TST) for hypogonadism causes prostate-cancer progression, a review of the contemporary literature provides evidence to the contrary. The prostate saturation model suggests that the androgen receptor (AR) is saturated at serum testosterone levels of 150-200 ng/dl, and that additional serum testosterone above this level has limited, if any, effects within the prostate. Indeed, studies in the modern era of PSA assessments indicate that TST does not affect prostate size, intraprostatic testosterone levels, or prostate-cancer progression, provided the baseline serum testosterone level is greater than this AR saturation point. However, the body of data on this subject comes from a small number of cases, and TST should only be administered to patients with prostate cancer after thorough discussions of the risks and benefits, with subsequent careful monitoring.

Curr Urol Rep. 2014 Jul;15(7):422. doi: 10.1007/s11934-014-0422-5.

To treat or not to treat with testosterone replacement therapy: a contemporary review of management of late-onset hypogonadism and critical issues related to prostate cancer.

Kava BR1.
Author information

Abstract

Over the last 10 years there has been a dramatic increase in the number of patients identified and treated with testosterone replacement therapy (TRT) for late-onset hypogonadism (LOH). By virtue of age, race, and family history, many of these patients are concurrently at risk for harboring indolent prostate cancer. Other men are at increased risk for prostate cancer as a result of an elevated serum PSA level or having had a prior prostate biopsy showing prostatic intraepithelial neoplasia (PIN) or atypical small acinar proliferation (ASAP). The clinician is often challenged with the decision whether to initiate TRT in these patients. This review presents a contemporary overview of the rationale for TRT, as well as the relationship between testosterone (endogenous and exogenous) and premalignant and malignant lesions of the prostate. We will discuss preliminary data from several recent series demonstrating that TRT may be safely administered in select patients with certain premalignant and bona fide malignant tumors of the prostate. In the absence of a large randomized clinical trial with long-term outcome data evaluating TRT, we hope that this overview will provide clinicians with an evidence-based approach to managing these anxiety-provoking - and often frustrating - clinical scenarios.

Prostate Cancer Prostatic Dis. 2014 Jun;17(2):132-43. doi: 10.1038/pcan.2013.60. Epub 2014 Jan 21.
The effect of testosterone replacement therapy on prostate cancer: a systematic review and meta-analysis.
Cui Y1, Zong H1, Yan H1, Zhang Y1.
Author information
Abstract
BACKGROUND: Testosterone replacement therapy (TRT) is a widely accepted form of treatment worldwide for aging men with late-onset hypogonadism syndrome. Urologists have been concerned about the possibility of TRT causing prostate cancer. The aim of this study was to assess the relationship between TRT and prostate cancer.
METHODS: A literature review was performed to identify all published, randomized controlled trials (RCTs) of testosterone treatment for hypogonadism. The search included the MEDLINE, Embase and the Cochrane Controlled Trials Register databases. Fixed-effect model was chosen for homogeneous studies; otherwise, a random-effect model was used. Inconsistency was quantified by using the I2 statistic, which tests the proportion of heterogeneity across studies.
RESULTS: Results of 22 RCTs involving a total of 2351 patients were analyzed. Eleven RCTs were short-term (<12 months) and 11 were long-term (12-36 months) comparisons of TRT with a placebo; TRT was administered transdermally, orally or by injection. Respective odds ratio (OR) and 95% confidence interval (CI) values for injection, transdermal administration and oral administration of short-term TRT were as follows: prostate cancer: 0.39 (0.06-2.45), 1.10 (0.26-4.65) and no oral; biopsy: 5.28 (0.24-113.87), 2.11 (0.32-13.73) and no oral; and prostate nodule: 1.01 (0.13-7.60), no injection and oral. Respective OR and 95% CI values for injection, transdermal administration and oral administration of long-term TRT were as follows: prostate cancer: 2.09 (0.18-24.73), 3.06 (0.12-76.70) and 0.19 (0.01-4.03); biopsy: 2.09 (0.18-24.73), 3.65 (0.88-15.20) and 0.97 (0.13-7.03); and prostate nodule: 3.13 (0.12-80.68), 1.00 (0.06-16.41) and 0.97 (0.13-7.03). Though for some routes of administration and some end points, the OR associated with testosterone administration were >1 indicating increased risk, none of these reached or even approached statistical significance (all P>0.10), which was consistent with the results of subgroup analyses and sensitivity analysis. Besides, sensitivity analysis indicated that short-term TRT was more likely to increase PSA levels than treatment with placebo (P<0.00001).
CONCLUSIONS: This meta-analysis shows that regardless of the administration method, TRT is the short-term safety and does not promote prostate cancer development or progression but long-term data are warranted with justifiable end points.

J Clin Endocrinol Metab. 2010 Jun;95(6):2560-75. doi: 10.1210/jc.2009-2575.

Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis.

Fernández-Balsells MM1, Murad MH, Lane M, Lampropulos JF, Albuquerque F, Mullan RJ, Agrwal N, Elamin MB, Gallegos-Orozco JF, Wang AT, Erwin PJ, Bhasin S, Montori VM.
Author information

Abstract

CONTEXT: The risks of testosterone therapy in men remain poorly understood.

OBJECTIVE: The aim of this study was to conduct a systematic review and meta-analyses of testosterone trials to evaluate the adverse effects of testosterone treatment in men.

DATA SOURCES: We searched MEDLINE, EMBASE, and Cochrane CENTRAL from 2003 through August 2008. Review of reference lists and contact with experts further identified candidate studies.

STUDY SELECTION: Eligible studies were comparative, randomized, and nonrandomized and reported the effects of testosterone on outcomes of interest (death, cardiovascular events and risk factors, prostate outcomes, and erythrocytosis). Reviewers, working independently and in duplicate, determined study eligibility.

DATA EXTRACTION: Reviewers working independently and in duplicate determined the methodological quality of studies and collected descriptive, quality, and outcome data.

DATA SYNTHESIS: The methodological quality of the 51 included studies varied from low to medium, and follow-up duration ranged from 3 months to 3 yr. Testosterone treatment was associated with a significant increase in hemoglobin [weighted mean difference (WMD), 0.80 g/dl; 95% confidence interval (CI), 0.45 to 1.14] and hematocrit (WMD, 3.18%; 95% CI, 1.35 to 5.01), and a decrease in high-density lipoprotein cholesterol (WMD, -0.49 mg/dl; 95% CI, -0.85 to -0.13). There was no significant effect on mortality, prostate, or cardiovascular outcomes.

CONCLUSIONS: The adverse effects of testosterone therapy include an increase in hemoglobin and hematocrit and a small decrease in high-density lipoprotein cholesterol. These findings are of unknown clinical significance. Current evidence about the safety of testosterone treatment in men in terms of patient-important outcomes is of low quality and is hampered by the brief study follow-up.

Does testosterone therapy benefit older men? (i)

TABLE 3. Ability to maintain erection during intercourse

Treatment	0 month	3 months	6 months	*P* value, mean change DHT *vs.* placebo
Placebo	2.53 ± 1.44	2.65 ± 1.56	2.81 ± 1.56	0.04
DHT	2.26 ± 1.41	2.70 ± 1.50	3.24 ± 1.35	

Difficulties in maintaining erection during intercourse were scored from 1–6: 1, always; 2, in 75% of intercourses; 3, in 50%; 4, in less than 25%; 5, in less than 10%; and 6, never.

Kunelius P, Lukkarinen O, Hannuksela ML, Itkonen O, Tapanainen JS. The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. J Clin Endocrinol Metab. 2002 Apr;87(4):1467-72.

Does testosterone therapy benefit older men? (ii)

Corona G, Rastrelli G, Maggi M. Diagnosis and treatment of late-onset hypogonadism: systematic review and meta-analysis of TRT outcomes. Best Pract Res Clin Endocrinol Metab. 2013 Aug;27(4):557-79.

Late-onset hypogonadism (LOH) is a relatively common conditions affecting the aging male. The aim of this review is to summarize the available evidence regarding LOH and its interaction with general health. LOH is often comorbid to obesity and several chronic diseases. For this reason lifestyle modifications should be strongly encouraged in LOH subjects with obesity, type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS) and good treatment balance of chronic diseases. Medical therapy of LOH should be individualized depending on the etiology of the disease and the patient's expectations. *Available evidence seems to suggest that testosterone replacement therapy is able to improve central obesity (subjects with MetS) and glycometabolic control (patients with MetS and T2DM), as well as to increase lean body mass (HIV, chronic obstructive pulmonary disease), along with insulin resistance (MetS) and peripheral oxygenation (chronic kidney diseases). However,*

. . . it should be recognized that the number of studies on benefits of T supplementation is too limited to draw final conclusions. ***Longer and larger studies are needed to better clarify the role of TRT in such chronic conditions.***

Does testosterone therapy benefit older men? (ii.1)

Total T	Effect
150-200 ng/dL	weakness, loss of muscle mass, erectile dysfunction

Caveat emptor (Let the buyer beware. . .)

Corona G, Rastrelli G, Maseroli E, Forti G, Maggi M. Sexual function of the ageing male. Best Pract Res Clin Endocrinol Metab. 2013 Aug;27(4):581-601.

With the progressive increase in the proportion of older people, there is an increasing interest in characterizing the modifications of sexual health and the effect of its perturbations as a function of the aging process. The aim of this review is to summarize the available evidence regarding the age-dependent modifications of male sexual function and their interaction with general health and age-dependent modification of endocrine function. Elderly patients are often affected by multiple organic diseases which can interfere with sexual function. Despite this evidence, several studies have indicated that, with advancing age, normal erections are not an absolute prerequisite to remain sexually active. Good physical health, the availability of a partner, and a regular and stable pattern of sexual activity earlier in life predict the maintenance of sexual activity in old age. Conversely, *there are no convincing data that hormonal changes, associated with aging, have a primary role in underlying changes in sexual function in healthy aging men*. Nonetheless, sexual dysfunctions especially in elderly people are poor investigated. Asking about sexual health remains difficult or embarrassing for many primary care physicians. In addition, many patients find it difficult to raise sexual issues with their doctor. This situation often results in sexual issues not being adequately addressed thus resulting in depression, social withdrawal and delayed diagnosis of underlying medical conditions often resulting in forthcoming cardiovascular events. Education and permission from a health care professional may help to alter such misconceptions. Information from physicians regarding normal age-related changes in sexuality and encouragement, together with advice on how to continue meaningful sexual relations, may play a key role in altering such negative attitudes.

Ultimately, the New Macho boils down to a simple principle: ***in a changing world, men should do whatever it takes to contribute their fair share at home and at work, and schools, policymakers, and employers should do whatever they can to help them. After all, what's more masculine: being a strong, silent, unemployed absentee father, or actually fulfilling your half of the bargain as a breadwinner and a dad?***

http://www.newsweek.com/why-we-need-reimagine-masculinity-71993

THE END