An Idea Whose Time Has Come-Male Health Programs: An Opportunity For Clinical Expansion and Better Health

KEVIN R. LOUGHLIN MD ,MBA
Harvard Medical School
Boston, MA

THE WEAKER SEX-MALES

- LIFE EXPECTANCY (YEARS)
- WHITE FEMALES-81
- WHITE MALES-78
- BLACK FEMALES-79
- BLACK MALES -76

FOOD FOR THOUGHT

APPROXIMATELY 20,000 GENES IN THE HUMAN GENOME

X CHROMOSOME CONTAINS 1098

HOW MANY GENES ON Y CHROMIOSOME?

78!

FOOD FOR THOUGHT

EVIDENCE THAT THE Y CHROMOSOME HAS LOST A THOUSAND GENES OVER THE PAST 300 MILLION YEARS

IN 14 MILLION YEARS THE Y CHROMOSOME MAY DISAPPEAR

NO MORE MEN, SO……

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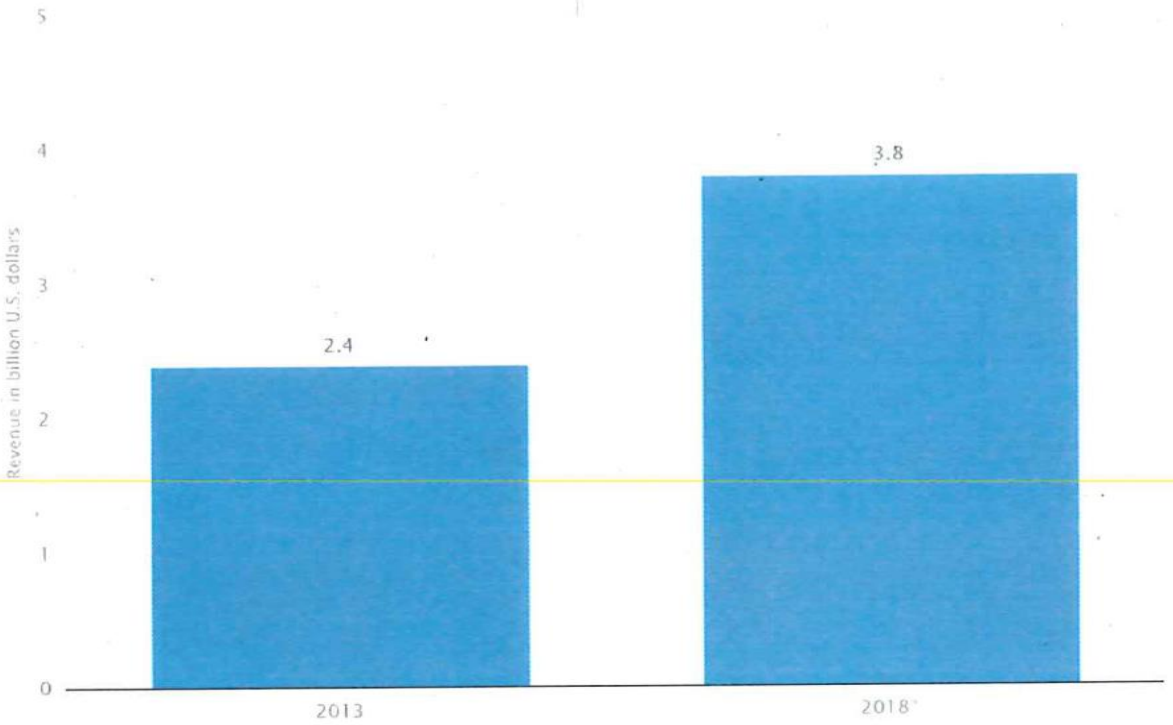
TESTOSTERONE

- Aging
- Cardiac
- Aggression
- Sports-Performance/Enhancing
- Reproduction
- Thrombosis
- Metabolic Syndrome-Glycemic Control
- Sexual Function
- Osteoporosis
- Prostate Cancer
- BPH
- Women
- Libido
- Andropause
- Atherosclerosis
- Anemia
- Baldness
- Obesity
- AUA Position Statement
- Sleep Apnea

TESTOSTERONE

- Measurement –Age Adjusted
- Prostate Cancer
- Cardiac
- Sexual Function
- Summary T Trials
- AUA Position Statement

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



Show further information

Show sources information

Data visualized by tableau

ABOUT THIS STATISTIC

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

Show more

SPECIAL FUNCTIONS

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+ Varian Medical Systems' annual revenue 2011 to 2016

+ Cardinal Health's annual revenue 2011-2016

+ Annual revenue of American Addiction Centers 2011-2016

TESTOSTERONE FRACTIONS(MALE UNDER 40)

Free Testosterone	2%
Weakly Bound to Albumin	68%
Tightly Bound to SHBG	30%

SHBG increases with aging

1% Decline/Yr	Total T
2% Decline/Yr	non-SHBG bound T (free T)

LABORATORY DIAGNOSIS OF TESTOSTERONE DEFICIENCY

PREVELANCE (Age 30-79 5.6%
(TT<300ng/dl)

30% with abnormal T, report is WNL

Morning T

RIA
Liquid Chromotography/Mass Spectrometry

If ABNL-Repeat with FSH, LH, PRL

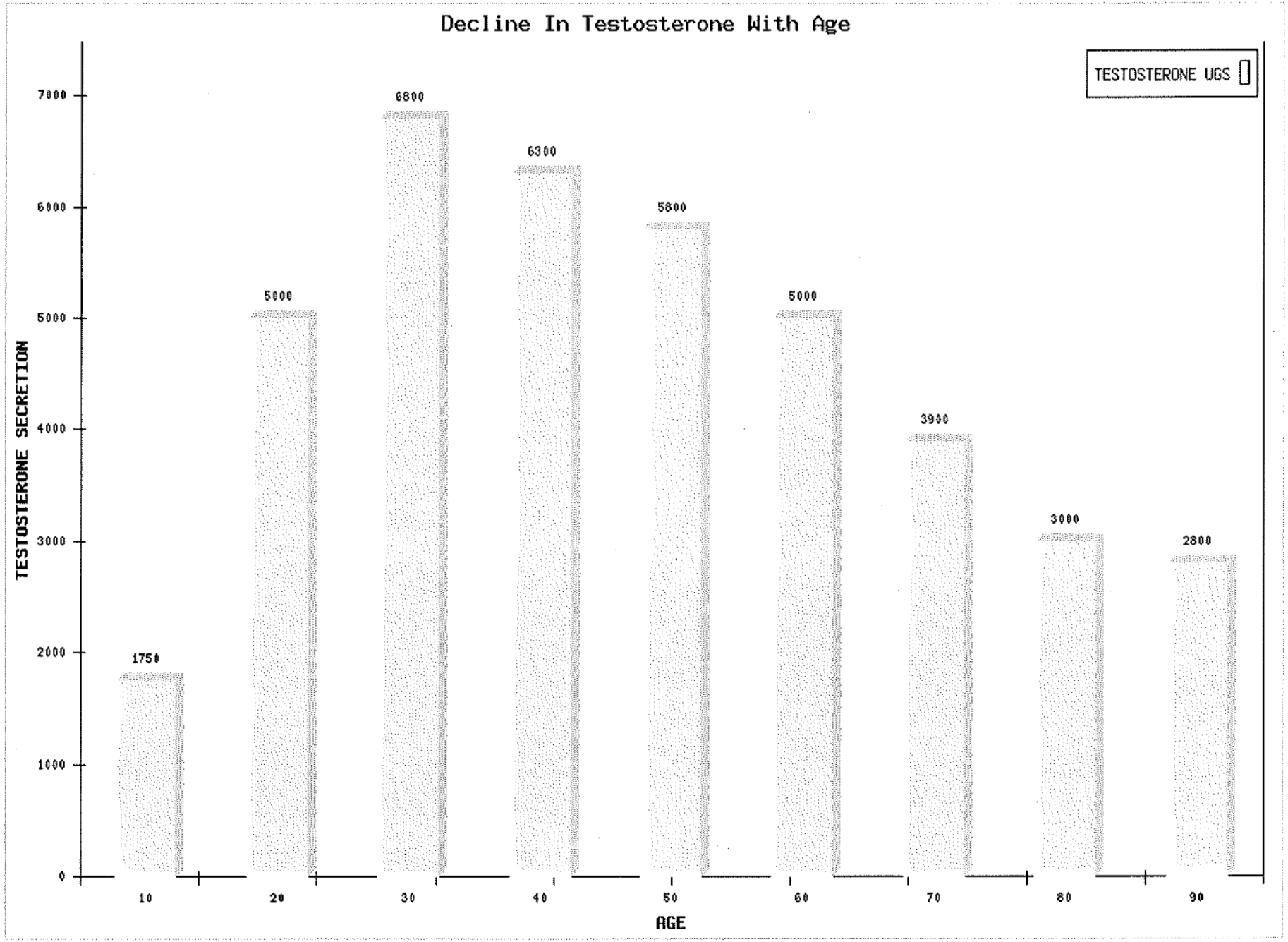
AVERAGE HORMONE LEVELS BY AGE IN MEN

Unit Conversion Calculator (/hormone-unit-conversion-calculator.html)

Vermeulen, A. (1996). **Declining Androgens with Age: An Overview.** (https://books.google.ca/books?id=efEnl1VdmtsC&lpg=PP1&pg=PA4#v=onepage&q&f=false) In Vermeulen, A. & Oddens, & B. J. (Eds.), *Androgens and the Aging Male* (pp. 3-14). New York: Parthenon Publishing.

Measurements in SI Units

Age	Total T (nmol/L)	Free T (pmol/L)	SHBG (nmol/L)	DHEA-S (umol/L)	Estradiol (pmol/L)
25-34	21.4	428	35.5	6.4	137
35-44	23.1	356	40.1	6.0	134
45-54	21.0	314	44.6	4.8	142
55-64	19.5	288	45.5	3.2	129
65-74	18.2	239	48.7	2.6	132
75-84	16.3	207	51.0	1.2	139
85-100	13.0	186	65.9	1.2	136


Decline In Testosterone With Age
TESTOSTERONE UGS
TESTOSTERONE SECRETION
7000
6000
5000
4000
3000
2000
1000
0
1750
5000
6800
6300
5800
5000
3900
3000
2800
10
20
30
40
50
60
70
80
90
AGE

TESTOSTERONE REPLACEMENT

- Heterogeneity of Response
- Active Therapy-60%,66% reached normal range
- need for active monitoring
- only75% had a baseline T within the prior 12 months
- overlap of symptoms between hypogonadism and normal aging
- Wu, “symptoms in aging men are nonspecific”
- “eugonadal”-should be age adjusted
- age adjusted-PSA,Creatnine, RF, ANA

Selective Use of Testosterone Therapy

Loughlin KR, Klap J

J.Urol., August 2016

Implications And Interpretations of Differences in Age Adjusted Testosterone Levels

Loughlin, KR

JAMA 2017; 177(5):744

TESTOSTERONE AND PROSTATE CANCER

- The Relationship Between Total Testosterone Levels And Prostate Cancer: A Review Of The Continuing Controversy

  -Klap J, Schmid M, Loughlin KR, J. Urol, 2015

  18 Studies –CaP+ Low T level

  17 Studies-CaP+ High T level

  10 Studies-No Relationship to T level

TESTOSTERONE AND PROSTATE CANCER

The Testosterone Conundrum: The Putative Relationship Between Testosterone Levels And Prostate Cancer

-K.R. Loughlin

-Urologic Oncology 2016

1. METHODOLOGY ISSUES
2. DISCOURDANCE BEWTEEN SERUM T AND INTRAPROSTATIC T
3. ROLE OF THE ANDROGEN RECEPTOR
4. INFLUENCE OF CHRONIC TESTOSTERONE LEVELS

Dynamic Patterns of Testosterone Levels Within Individuals And Risk of Prostate Cancer Amoung Hypogonadal Men: A Longitudinal Study

Xu, X et al
J. Urol, online October 2017

376 untreated hypogonadal men

followed for 12 yrs

1) Coefficient of variation (cv)
2) Ratio of largest decline relative to the mean (MMDRM)
3) Median of maximum declines (MMD)

The later a male's T dropped below 12.1 nmol/L and the dynamic T level variations conferred an increase risk (HR from 2.70 to 8.45)

Commentary

-Some CaP should be considered a chronic disease

-NCI SEER-Median age -66yo

10.1% are 54 y.o. or younger

-Autopsy series-30% of men in their 30s had CaP foc

-A Post-hoc T not informative

-single glucose and DM

-single BP and Htn

-Loughlin, KR

-J. Urol, online October 2017

CAN YOU GIVE EXOGENOUS T TO A PATIENT WITH KNOWN CAP?

PRO+CON J. UROL, 2016

MORGENTALER, GLEAVE, KLOTZ

PRO

-MEN WHO RECEIVE EXOGENOUS T APPEAR TO HAVE NO GREATER RISK

-SATURATION MODEL “250NG/d/

CON

-SYMPTOMS OF HYPOGONADISM-SEEN WITH BOTH LOW T AND NL T

-NOT CLEAR CUT

-ANDROGEN RECEPTOR

-ACCELERATOR OF CaP

-MANY UNDERPOWERED STUDIES

-SATURATION MODEL-OVERLY SIMPLISTIC

-MORE THAN 1,000 m RNA and proteins regulated by AR

-IF SATURATION MODEL APPLIED TO BENIGN TISSUES, THERE WOULD BE NO SYMPTOMATIC OR METABOLIC BENEFIT TO TRT

Testosterone Therapy In Patients With Treated And Untreated Prostate Cancer : Impact On Oncologic Outcomes

Ory J et al, J.Urol,2016

82 Hypogonadal Men With CaP

Treated with T

50XRT

22 RP

8AS

1CRYO

1HIFU

Median age 75.5 yo. Median F.U.-41 mos

50XRT-3 Biochemical Recurrence

22RP-0 Biochemical Recurrence

8AS-⬆PSA, but no Gleason upgrade

-Appears Safe

TESOSTERONE AND CARDIAC EVENTS

1. VIGEN ET AL JAMA 2013

-VA System

-MI, Stroke, Death higher in T group

-T<300 ng/dl

-T vs untreated

-methodological concerns

-2 officials corrections 1/15/14,3/5/14

FDA-"Given the described limitations of the study by Vigen et al it is difficult to attribute the reported findings to testosterone treatment."

2. FINKLE ET AL PLoS One 2014

-Retrospective health insurance data base

-Rates of non fatal MI up to 90 days after T prescription and compared to MI rates in the previous 12 months

-No information regarding CV risk factors such as DM, Htn,Hyperlipidemia, smoking, obesity

-MI endpoint-solely insurance diagnosis code

-selection bias

-short T exposure 30-90 days

-FDA "difficult to attribute to increased risk to testosterone alone"

3. BASARIA ET AL NEJM, 2010

-156 randomized to receive 7.5gm of gel x 3yrs

-152 randomized to placebo x 3yrs.

-60 yrs and above

-Benefit of T over placebo for muscular and functional responses

-Terminated because of “cardiovascular” events in treatment arm

-Most frequent adverse event-pedal edema

-4 major adverse cardiac events (MACE)

-death, 2M.I.s, 1 stroke-all in T group

FDA: “non-conclusive because of the small sample size and small number of events reported in the study…..the differences may have been due to chance alone.

4. XU ET AL BMC Medicine 2013

-Meta –analysis of CV events in 27 placebo-controlled T studies of 12 wks or more

-2 of the 27 studies contributed to 35% of all CV events

-Corona ET AL Expert Opin. Drug Safety, 2014 meta-analysis in 75 studies no association

5. BUDOFF ET AL JAMA 2017

Testosterone Treatment And Coronary Artery
Plaque Volume In Older Men With Low T

-T treatment associated with significantly greater increase in non calcified plaque volume (p=.003)

-138 men (73T, 65 placebo)

-baseline 70(50.7%) had coronary calcification

- “Larger studies are needed to understand the clinical implications of this finding.”

6. SHARMA ET AL

Normalization of testosterone level is associated with reduced incidence of myocardial infarction mortality in men
Eur. Heart J. 2015

83,010 men

Three Groups 1) TRT with normalization of TT
2) TRT without normalization of TT
3) Did not receive TRT

Significant advantage for all-cause mortality, MI and Stroke in Group 1, no difference between Groups 2 and 3

SUMMARY OF THE TESTOSTERONE TRIALS

TESTOSTERONE -SMALL INCREASE IN SEX ACTIVITY

-SMALL IMPROVEMENT IN E.D.

-SLIGHTLY IMPROVED MOOD

-NO DIFFERENCE IN 6 MIN WALKING DISTANCE

-SNYDER ET AL, NEJM 2016

TESOSTERONE -NO IMPACT OF MEMORY IMPAIRMENT

-INCREASE IN CORONARY CALCIFICATION

-IMPROVEMENT IN BONE MINERAL DENSITY

-IMPROVEMENT IN HGB LEVELS

FOLLOW –UP NOT LONG ENOUGH TO MEASURE DIFFERENCES IN CARDIAC EVENTS, FRACTURES OR MORTALITY

-FOUR ARTICLES IN JAMA, 2017

ERECTILE DYSFUNCTION AND TESTOSTERONE

RELATIONSHIP BETWEEN TESTOSTERONE AND ERECTILE DYSFUNCTION

-Jacob Rajeer, Review In Urology 2000

NOT ALL ED HAVE LOW T

NOT ALL LOW T HAVE ED

DO NOT TREAT WITH T UNLESS VERIFY LOW T

DATA DEMONSTRATE THAT FREE T LEVELS AT AGE 75 ARE 50% OF THOSE FOUND AT AGE 25

NORMAL ADULT T LEVELS ARE NOT NECESSARY FOR NORMAL ERECTIONS

WEIGH POTENTIAL RISKS

CLINICAL ED-20-40% WILL HAVE A LOW FREE T

EFFECTS OF TESTOSTERONE TREATMENT IN OLDER MEN -Snyder PJ et al, NEJM,2016

Sexual Function Trial

Greater Increase in T level associated with greater increment in PDQ-Q4 score

Increased Sexual Desire

Increased Erectile Function (by IIEF)

AUA Position Statement on Testosterone Therapy

Board of Directors, Feb 2014
Board of Directors, August 2015 (revised)

- Conflicting evidence on impact of T therapy on cardiovascular risks
- Patients should understand the need for monitoring
- Testosterone therapy in absence of hypogonadism is inappropriate
- Only FDA-approved medications should be used; over –the-counter preps generally should be avoided
- Many of the symptoms are non-specific and may be multifactorial in origin
- T therapy should not be offered to men with normal testosterone levels.
- Adverse side effects should be discussed: acne, breast swelling, erythocytosis, swollen ankles, reduced testicular size, infertility
- No definite answers on risk of CaP and Cardiovascular disease and patients should be informed
- Optimal follow up not defined, but should include Hct, PSA, T level