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

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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 CHROMOSOME?
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..................
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.................
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)

ABOUT THIS STATISTIC
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.

SPECIAL FUNCTIONS
Download as...
- Graphic (PNG)
- Excel (XLS)
- PowerPoint (PPT)
- PDF

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Data visualized by Tableau

Show sources information

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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)


<table>
<thead>
<tr>
<th>Age</th>
<th>Total T (nmol/L)</th>
<th>Free T (pmol/L)</th>
<th>SHBG (nmol/L)</th>
<th>DHEA-S (umol/L)</th>
<th>Estradiol (pmol/L)</th>
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</tbody>
</table>
Decline In Testosterone With Age

AGE

TESTOSTERONE SECRETION

10 20 30 40 50 60 70 80 90
TESTOSTERONE REPLACEMENT

• Heterogeneity of Response
• Active Therapy-60%, 66% reached normal range
• need for active monitoring
• only 75% 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, Creatinine, 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

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 BETWEEN 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 Among 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


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

TESTOSTERONE
- 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)
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