

Testosterone

1

Not just a male hormone

- Male-ness Protects Female-ness
- Anti-proliferative at the breast and prostate
Metabolite 3-B-DIOL anti-cancer action
- Protects heart cells, hippocampus, and more

2

Monitoring T

Reference Ranges Not Optimal

- Recent guidelines use the terms “physiological dosing” and “physiological levels” when making recommendations for T therapy.
- However, this is counterintuitive to physiology—the major source of bioavailable T in women is unmeasurable and not reflected in serum T levels.
- “Physiological dosing” may be why T therapy—effectively raising T levels into the mid to high physiological range—has proven clinically ineffective in some studies.
- T’s effect is dose dependent, and there is no evidence (i.e., drug concentration in blood studies), or documented adverse events, supporting the “opinion” that serum T levels on therapy should remain within endogenous or “physiological” ranges—concentration/dose–response studies support the opposite.
- Beneficial effects of testosterone therapy in women measured by the validated Menopause Rating Scale (MRS). *Maturitas*. 2011;68:355–361.
- Testosterone implants in women: Pharmacological dosing for a physiologic effect. *Maturitas*. 2013;74:179–184.
- Testosterone dose-response relationships in hysterectomized women with and without oophorectomy: Effects on sexual function, body composition, muscle performance and physical function in a randomized trial. *Menopause* (New York, NY). 2014; 21:612–73.
- Dose-dependent effects of testosterone on sexual function, mood, and visuospatial cognition in older men. *J Clin Endocrinol Metab*. 2005;90(7):3338–3840.

Berkson Copyright

3

3

Gut

- In the gut T signaling improves immunity
- By increasing SIgA
- Microbiome creates androgens (male hormones) to protect gut wall and gut immunity by enhancing SIgA

4

Stomach

- In the parietal cell, T goes to E
- Which goes to the liver and
- Up-regulates detox to caretake all hormones metabolized in the liver
- Thus testosterone and estrogen are greatly involved in liver detoxification

- **Biochemical Pharmacology** Volume 84, Issue 1, 1 July 2012, Pages 93-103
- **Estradiol induces cytochrome P450 2B6 expression at high concentrations: Implication in estrogen-mediated gene regulation in pregnancy**
Gastroenterology Volume 90, Issue 2, February 1986, Pages 299-305
- **Effects of portal vein ligation on sex hormone metabolism in male rats: Relationship to lowered hepatic cytochrome P₄₅₀ levels**

5

T metabolism

- T is metabolized to DHT
- This is metabolized to 3-beta Diol
- Up-regulates ER beta
- ER beta is the anti-cancer estrogen
- Protects against breast, prostate, lung and other cancers And all tissues where there is ERB
- T can also go to E and activate estrogen receptor

6

Femaleness Has Always Needed Maleness

- In the beginning estrogen could not signal without 3-beta diol
- The first estrogen had a receptor
- But no hormone to signal it
- It took thousand more years to produce estrogen as it's so complicated
- The simpler archival 3-Beta Diol came to the rescue, so the first estrogen signal was cooperation between T and Estrogen Receptor
- ME Baker Univ SF & SD

7

Genders

- Both genders have same hormones and same T
- But men make 7 to 10 times more in the blood
- Causing 20 times higher metabolic rate
- But women are more sensitive to male hormones 😊

8

T Actions

- Protects the brain especially hippocampus
- Tamps down APOE4 vulnerability gene
- Protects bone
- Promotes healthier insulin sensitivity as low T linked to IR
- Boosts gut wall immunity as boosts SIgA
- T levels inversely related to arterial stiffness; the more T the healthier the heart/blood vessels.
- Atherosclerosis 2009;207:318-327
- J Clin Metabol 2010; 95:1123-1130

9

Males

- Low testosterone is associated with increased risk of death from any which way (all cause mortality)
- T levels inversely related to heart disease and cancer deaths.
- Eur Heart J 2010;31 (12):1494-1501

10

Males

- Higher levels of T linked to lower heart attack occurrence.
- HDL and free T decrease as we age
- Higher T correlates with higher levels of good cholesterol
- T exerts anti-atherogenic effect
- Biochem Biophys Commun 2002
Sept6:296(5):1051-7

11

Estrogen Levels

- Increase as males age.
- If T is lowering and E is increasing, feminization.
- Increased aromatase activity with fatigue, stress, disease, age
- Obesity – fat cells make estrogen
- Excessive alcohol
- Environmental Estrogens
- Zinc deficiency (and other minerals)
- B vitamin Deficiencies
- Processed foods, heated fats,
- Aging gut so can't absorb minerals
- Microbiome damaged so contributes less T

Peripheral production needs enzymes damaged by EDCs
Exp Clin Endocrinol Diabetes 119 2011 (8):490-96

12

Phone: (805) 836-1025
Fax: (805) 633-9256

FASTING: YES

▲ TESTOSTERONE, FREE, BIOAVAILABLE AND TOTAL, MALES (ADULT), IMMUNOASSAY

Analyte	Value	
▲ TESTOSTERONE, TOTAL, MALES (ADULT), IA	100 L	Reference Range: 250-827 ng/dL
ALBUMIN	4.2	Reference Range: 3.6-5.1 g/dL
SEX HORMONE BINDING GLOBULIN	36	Reference Range: 22-77 nmol/L

TESTOSTERONE, FREE

Analyte	Value	
---------	-------	--

13

TESTOSTERONE, FREE	See below	Reference Range: 6.0-73.0 pg/mL
TESTOSTERONE, BIOAVAILABLE		Reference Range: 15.0-150.0 ng/dL

Due to the diminished accuracy of immunoassay at levels below 250 ng/dL, calculations of the Free and Bioavailable Testosterone are not accurate. If needed, Testosterone, Free, Bio and Total, LC/MS/MS (test code 14966) is the recommended assay. This specimen must be collected in a red-top tube with no gel.

14

DIHYDROTESTOSTERONE	
Analyte	Value
DIHYDROTESTOSTERONE, LC/MS/MS	50 Reference Range: 12-65 ng/dL
<small>This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics Nichols Institute San Juan Capistrano. It has not been cleared or approved by FDA. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.</small>	
ESTRONE	
Analyte	Value

15

Case Report

- T levels increased but no improvement of joint pain
- Until added
- Receptor Detox
- Hormone Balance and Protect
- High dose niacinamide (work of William Kaufman MD)

16

Assessing Male

- Total and free T
- Total ideally over 650
- Free ideally above 65
- Bioavailable above 100
- SHBG
- FSH (**Elevated means testicles damaged due to chemotherapy, radiation, infection, alcohol abuse, processed foods, EDCs**)
- LH **causes the testicles to make testosterone, which is important for producing sperm.** Elevated means testicles not responding to T. Low levels may mean pituitary is not making enough.
- **Iodine – serum – around 100 mcg/L**

17

Sperm counts are down by 40-50%

- Are today's men more feminized than any other males before them?
- What does this do for their own health
- Their relationship and family health?
- But in assessing males, even teens these days, especially if overweight and not adequate muscle and anxiety etc. need to measure T as well as estradiol, estrone and progesterone.
- Hagai Levine et al, Temporal trends in sperm count: a systematic review and meta-regression analysis, *Human Reproduction Update* (2017). DOI: [10.1093/humupd/dmx022](https://doi.org/10.1093/humupd/dmx022)

18

Excess Estrogen in Men

- Less desire
- Less emotional stability
- Less stomach acid (GERD)
- Poorer digestion
- Increased sticky platelets
- Arteries less healthy, more jagged
- Increased risk of clots
- Increased risk of stroke, MI, predictive of hypertension, Type-2 diabetes,

19

T supports the health of our males

- In men with heart failure, low androgens linked to adverse prognosis.
- Heart 2010:96:504-509
- For each 6 ng/dc increase of T per liter of blood, 14% drop in risk of death
- And remember, T counts are lowering independent of age, well proven and replicated.
- Circulation 2007:116(23):2694-2701.

20

Need T

- Low levels of total T, free T and bioavailable T are associated with increased mortality from all causes, heart disease and cancer.
- Severity of heart disease is inversely correlated with levels of T.
- Taking T reduces blood sugar, HBA1C, and IR in diabetic and pre-diabetic men.

21

T – ApoE4

- Results support the hypothesis that APOE-ε4 status increases susceptibility to other risk factors, such as low testosterone, which may ultimately contribute to cognitive decline or dementia.

Neurobiol Aging. 2014 Jul;35(7):1778.e1-8.
Interaction of APOE genotype and testosterone on episodic memory in middle-aged men.

22

Nature Values T

- It protects the brain
- Reduces expression of gene that puts the brain at risk of Alzheimer's disease (ApoE4 gene)

23

T - Cognition

- Reduction in testosterone levels in men during aging is associated with cognitive decline and risk of dementia.
- Forty-four men were administered a battery of neuropsychological tests to establish the baseline prior to being randomly divided into two groups. The first group (Group A) received 24 weeks of testosterone treatment (T treatment) followed by 4 weeks washout, and then 24 weeks of placebo (P); the second group (Group B) received the same treatments, in reverse
- Our findings indicate a modest improvement on global cognition with testosterone treatment.

CNS Neurol Disord Drug Targets. 2016;15(3):337-43.

The Effects of Testosterone Supplementation on Cognitive Functioning in Older Men.

24

EDCs - T

- Many EDCs tamp down T signals and contribute to brain damage.
- Is gender bending due to feminization of more
- Estrogenic acting chemicals + many anti-androgenic chemicals
- JAMA Neurol. 2014 Sep;71(9):1189-90. doi: 10.1001/jamaneurol.2014.795.
- **Testosterone as the missing link between pesticides, Alzheimer disease, and Parkinson disease.**

25

Testosterone boosts SIgA

- Effect of exercise on the level of immunoglobulin a in saliva. *Biol Sport.* 2012 Dec;29(4):255-61. doi: 10.5604/20831862.1019662. Epub 2012 Nov 15. PMID: 24868115; PMCID: PMC4033058.
- chewing gum has large effects on salivary testosterone, estradiol, and secretory immunoglobulin A assays in women and men. *Psychoneuroendocrinology.* 2010 Feb;35(2):305-9. doi: 10.1016/j.psyneuen.2009.06.009. Epub 2009 Jul 16. PMID: 19615825.
- Testosterone is positively and estradiol negatively associated with mucosal immunity in Amazonian adolescents. *Am J Hum Biol.* 2019 Sep;31(5):e23284. doi: 10.1002/ajhb.23284. Epub 2019 Jul 5. PMID: 31273877.

26

Testosterone protects gut

- **Aim:** To investigate the role of sex hormones in the early postoperative complications of gastrointestinal diseases.
- **Methods:** A total of 65 patients who underwent operations for gastric and colorectal diseases (mainly malignant diseases) were included in the study. Peripheral venous blood samples were collected at different times for analysis of estradiol, testosterone and progesterone. The only study endpoint was analysis of postoperative complications.
- **Results:** Patients of both sexes were uniform but postoperative complication rate was significantly higher in female patients ($P = 0.027$). There was no significant association of estradiol and progesterone with postoperative complications.
- Testosterone levels in complicated patients were significantly lower than in uncomplicated patients ($P < 0.05$). Area under the receiver operating characteristic curve showed that a lower value of testosterone was a predictor for higher complication rate ($P < 0.05$), and a lower value of testosterone at later times after surgery was a better predictor of complications.
- **Conclusion: Patients with low testosterone level were prone to higher postoperative complications, which was evident in both sexes.**
- Does testosterone prevent early postoperative complications after gastrointestinal surgery? World J Gastroenterol. 2009 Nov 28;15(44):5604-9. doi: 10.3748/wjg.15.5604. PMID: 19938202; PMCID: PMC2785943.

Dr. Berkson© 2018

27

Mother's Milk SIgA

- Breastfeeding protects infants against infections **mainly via secretory IgA (SIgA) antibodies**, but also via other various bioactive factors.
- It is striking that the defense factors of human milk function without causing inflammation; some components are even anti-inflammatory.
- Protection against infections has been well evidenced during lactation against, e.g., acute and prolonged diarrhea, respiratory tract infections, including otitis media, urinary tract infection, neonatal septicemia, and necrotizing enterocolitis.
- **The need to encourage breastfeeding is therefore justifiable, at least during the first 6 months of life, when the infant's secretory IgA production is insignificant.**
- Immunology of breast milk. Rev Assoc Med Bras (1992). 2016 Sep;62(6):584-593. doi: 10.1590/1806-9282.62.06.584. PMID: 27849237.

Dr. Berkson© 2018

28

SigA

- The vast surfaces of the gastrointestinal, respiratory, and genitourinary tracts represent major sites of potential attack by invading microorganisms.
- **Immunoglobulin A (IgA), as the principal antibody class in the secretions that bathe these mucosal surfaces, acts as an important first line of defense**
- The function of immunoglobulin A in immunity. J Pathol. 2006 Jan;208(2):270-82. doi: 10.1002/path.1877. PMID: 16362985.

Dr. Berkson© 2018

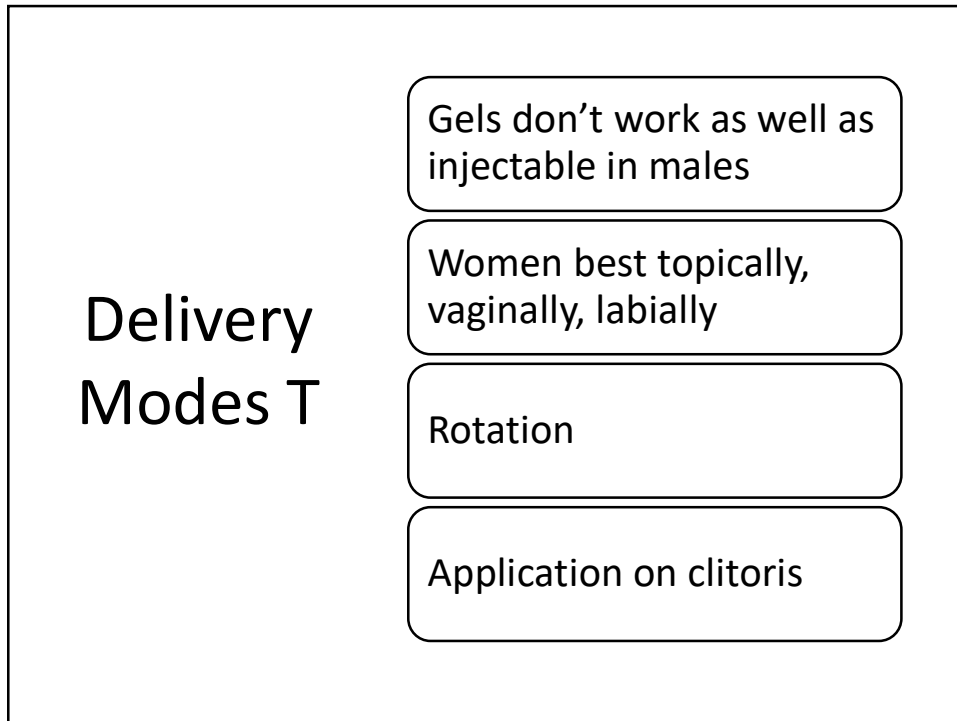
29

Increase T

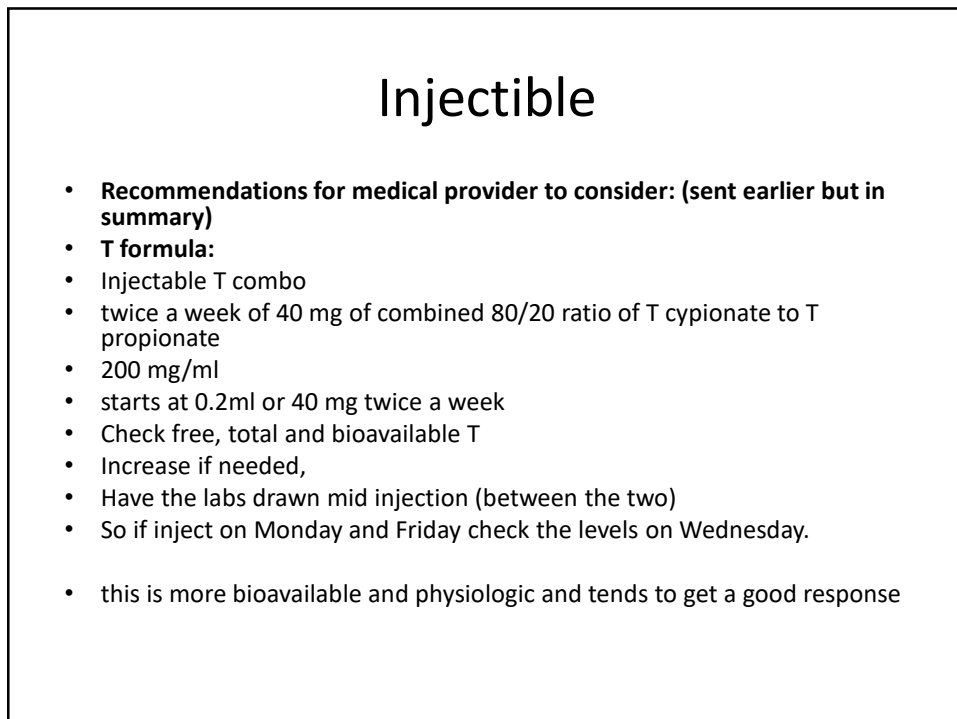
- Resistant Exercise
 - Making love
 - B-vital
 - T replacement
-
- Sexy Brain Awakened
Medicine Press Berkson DLB



30



31



32

T replacement

- Autoimmune diseases as boost SIgA
- Autoimmune diseases 159 and all but kidney happen more in women
- Welcome to the genderome.
- Sex differences in inflammation, redox biology, mitochondria and autoimmunity. Redox Biol. 2020 Apr;31:101482. doi: 10.1016/j.redox.2020.101482. Epub 2020 Mar 4. PMID: 32197947; PMCID: PMC7212489.

33

Microgenderome

- Microbiome has been labeled the “microgenderome” in 2013 by Harvard.
- • Healthy microbiome produces testosterone that drives immune protection.
- • Some EDCs, such as dichlorodiphenyldichloroethylene
- • (DDE) and vinclozolin and its metabolites, may interfere with microbiome protection from gender-specific diseases through inhibition of the AR.
- Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocr Rev 2009; 30:293-342.
- Endocrine Disruptors 2:1, e964539; December 2014; Published with license by Taylor & Francis Group, LLC. The microbiome as a target for endocrine
- disruptors: Novel chemicals may disrupt androgen and microbiome-mediated autoimmunity
- Science. 2013 Mar 1;339(6123):1044-5. Immunology.

34

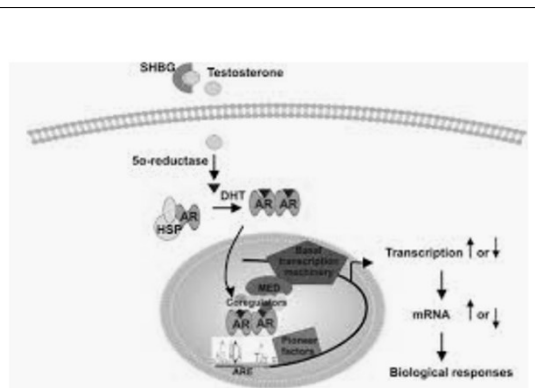
Why Males Have Less Autoimmune Diseases

- Testosterone is immune modulatory tamping down over-reactive immune responses.
 - T modulates gut immune system so not so easily into overdrive.
 - This is why all males and females, especially with autoimmune diseases, should be total T and free T tested along with SHBG.
 - You want a healthy higher normal level of T.
-
- Associations between male testosterone and immune function in a pathogenically stressed forager-horticultural population. *Am J Phys Anthropol.* 2016 Nov;161(3):494-505. doi: 10.1002/ajpa.23054. Epub 2016 Jul 28. PMID: 27465811; PMCID: PMC5075254.

Dr. Berkson© 2018

35

Androgen Receptor Under Attack by EDCs



- Androgen Receptor Genotype in Humans and Susceptibility to Endocrine Disruptors. *Horm Res Paediatr.* 2016;86(4):264-270. doi: 10.1159/000443686. Epub 2016 Feb 2. PMID: 26829394.

36

Low T

- Testosterone levels in American men have been declining steadily over the past two decades, a new study in the *Journal of Clinical Endocrinology and Metabolism* concludes.
- The reasons for this decline are unclear; the study suggests that neither aging nor changes in certain health factors, such as obesity or smoking, can completely explain the phenomenon.