Men's Health and Hormonal Axes

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First Some Hormone Basics

Back To The basics

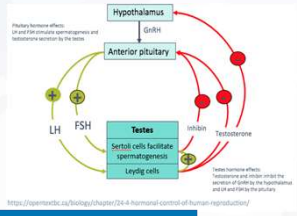
2

Physiology Recap

3

Simplified Look at Adult Male Hormones

- Kisspeptin hypothalamic complex receives input from the body, ie Leptin, cytokines, ?LPS
- Hypothalamus: Gonadotropin – releasing hormone (GnRH)
- Pituitary:
- FSH → Sertoli Cell → Sperm maturation, Inhibin-b
- LH → Leydig Cell Stimulation → Testosterone, *INSL-3



Man begins life with 700 million Leydig cells and loses six million of those cells yearly after his 20th birthday.

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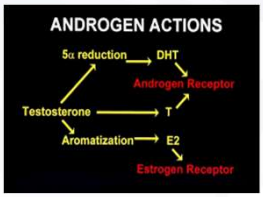
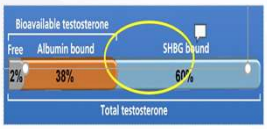
Testosterone Basics





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What Does T Do?

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The Many Roles of Testosterone

- Tissue Growth & Repair
- Male Reproduction/Sexual Health

Also

- Biomarker for comorbid diseases
- Immune modulation
- Adipocyte growth inhibition
- Energy metabolism
- Lipid and CVD health

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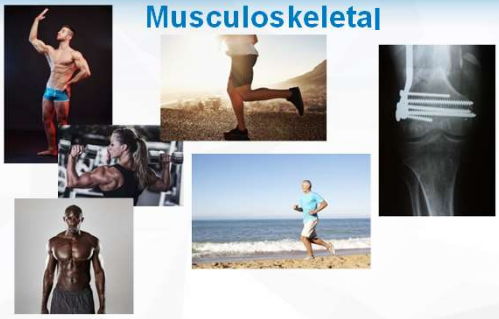
Musculoskeletal



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Testosterone the Androgenizer

Testosterone and other hormones are instrumental in-utero for primary and later on in puberty for secondary sexual development characteristics.

Testosterone is necessary for spermatogenesis, maintenance of secondary sexual characteristics, libido and erectile function

References:
1. Roth J, Grumbach M, Kaplan S. Effect of synthetic luteinizing hormone-releasing factor on serum testosterone and gonadotropins in prepubertal, pubertal and adult males. The Journal Of Clinical Endocrinology And Metabolism [serial online]. November 1973;37(5):680-686.
2. Morley,JE.1. Testosterone and behavior. Clinics in Geriatric Medicine [01 Aug 2003, 19(3):505-616
3. Li R, Meng X, Rao K, et al. Testosterone improves erectile function through inhibition of reactive oxygen species generation in castrated rats. PeerJ. May 3, 2016;4:e2000
4. D. Landry et al. Implications of leptin in neuroendocrine regulation of male reproduction, 2012 https://doi.org/10.1016/j.repbio.2012.12.001
5. A. Christine Kd nner 2012, Mapping Leptins Link to Reproduction. Molecular Medicine,(1) 2012 5-7.

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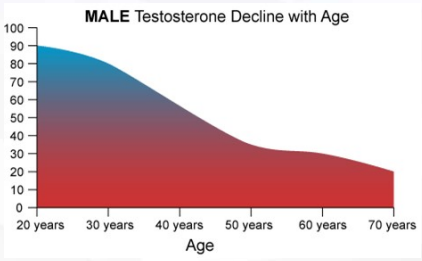
What is "Normal" MALE Testosterone Decline with Age



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Low T

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Clarifying Terminology

- Testosterone Deficiency (TD) = Low Testosterone
  - Replaced older term hypogonadism
- Testosterone Replacement Therapy (TRT)
  - Replaced recently by "testosterone therapy" (TT)

References: Morgentaler A, et al. *Mayo Clin Proc.* 2016; 91(7):881-896.

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TD: Definition

- Signs and symptoms consistent with low testosterone and low serum testosterone levels that may adversely effect QOL and multiple organ functions
  - Testosterone should be measured fasting, in the AM, using a reliable, accurate, and valid assay, then repeat the test to ensure the diagnosis
  - In men with total T near lower limit of normal or who have a condition that alters SHBG, recommend free T (reliable and accurate assay)

References:
1. Bhasin S, et al. *J Clin Endocrinol Metab.* 2018; 103(5): 1715-1744.
2. Morgentaler A, et al. *Mayo Clin Proc.* 2016; 91(7):881-896.

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TD: Diagnosis

- TD diagnosis should include the entire clinical picture aided by laboratory testing
- Rigid reliance on serum total testosterone has limitations
  - No study has documented a single testosterone threshold that reliably distinguishes those men with SS 2^0 to TD, from those men who do not

References: Morgentaler A, et al. *Mayo Clin Proc.* 2016; 91(7):881-896.

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TD: Etiology

- **Primary hypogonadism**
  - Testicular origin impacts T and fertility
  - Dx: low T, high LH/FSH
- **Secondary hypogonadism**
  - Hypothalamic-pituitary origin
  - Dx: low T, low or inappropriately nl LH/FSH
- **Mixed Hypogonadism**
  - Dual origin: testes, hypothalamic-pituitary
  - Dx: low T, mild increase LH/FSH (can vary)

References:
1. Surampudi P, et al. *Int J Endocrinol.* 2012; 1-21.
2. Dudek P, et al. *Menopause Rev.* 2017; 16(2): 66-69.

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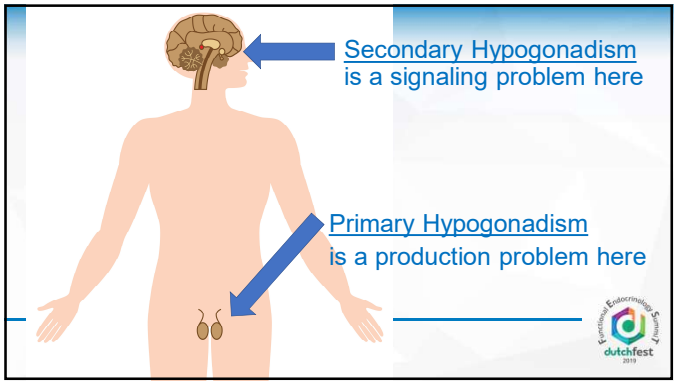

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Symptoms of Low T

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Low T Symptoms

- Belly Fat
- Bone Loss
- Low Energy
- Low Sex Drive
- Low Muscle Mass
- Mood Issues/Brain Fog
- Gynecomastia
- Erectile Dysfunction

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Low T Signs and Symptoms

- T symptoms more likely as T level decreases
  - Decreased libido: T level < 15 nmol/L (~ 433ng/dL)
  - Increased visceral fat: T level < 12nmol/L (~ 346ng/dL)
  - Depressed mood/ DM: T levels < 10nmol/L (~ 288 ng/dL)
  - Erectile dysfunction: T levels < 8nmol/L (230ng/dL)

Morgentaler A, et al. *Mayo Clin Proc.* 2016; 91(7):881-896.

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Low T Signs and Symptoms

Symptoms and associated morbidities	
Sexual function	Cognition and vitality
Loss of libido	Decline in verbal and visual memory
Erections: reduced quality and frequency, including nocturnal erections	Decline in visuospatial performance
Oligospermia or azoospermia	Depressed mood
Gynecomastia/breast discomfort	Decreased energy
Changes in secondary hair characteristics (e.g., shaving)	Decline in feelings of initiative
Changes in size of testes	Decreased sense of vitality
Decreased fertility	
Muscle, bone, and body composition	Other
Progressive decrease in muscle mass	Sleep disturbance
Decreased physical function	Lipid abnormalities
Decrease in bone mineral density; osteopenia, osteoporosis, increased risk of bone fractures	Mild anemia (normochromic, normocytic)
Increase in visceral fat	Decreased response to PDE5 inhibitors

Surampudi P, et al. *Int J Endocrinol.* 2012; 1-21.

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Low T in Young Men

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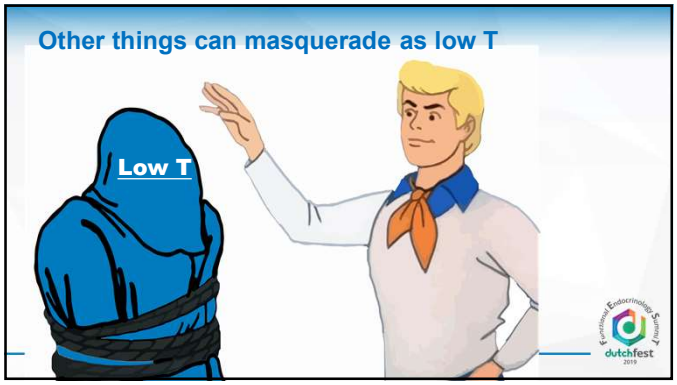
Other things can masquerade as low T
Low T

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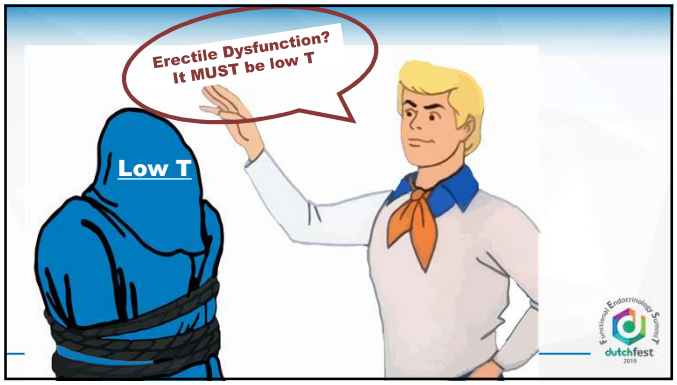
Erectile Dysfunction?
It MUST be low T
Low T

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Its was stress causing
those Low T symptoms!!!
Stress

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Lab Assessments for Low T in Young Men

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Primary Hypogonadism

High LH
Low T

Secondary Hypogonadism

Low or Low Normal LH
Low T

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TD on the Rise - A Growing Epidemic?

The average levels of the male hormone dropped by 1 percent a year, Dr. Thomas Travison and colleagues from the New England Research Institutes in Watertown, Massachusetts.

This trend also does not appear to be related to age.

References: Travison et al. **Secular Decline in Male Reproductive Function: Is Manliness Threatened?** The Journal of Clinical Endocrinology & Metabolism 92(1):44–45

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Causes of Low T in Young Men

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Potential Root Causes

- Hypothyroidism
- TBI (male patients in violent sports are at risk)
- Zinc deficiency (gut issues, malabsorption)
- Regular alcohol or THC use
- Removed testicle
- Environmental exposure
- Obesity
- Stress and/or sleep deprivation
- Medications (opioids, anabolic steroids)

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Urinary Phthalate Metabolites Are Associated With Decreased Serum Testosterone in Men, Women, and Children From NHANES 2011–2012

- **Results:** Multiple phthalates were associated with significantly reduced T in both sexes and in differing age groups. In females, the strongest and most consistent inverse relationships were found among women ages 40-60 years. In boys 6-12 years old, an interquartile range increase in metabolites of di-2-ethylhexyl phthalate was associated with a 29% (95% confidence interval, 6, 47) reduction in T. In adult men, the only significant or suggestive inverse associations between phthalates (metabolites of di-2-ethylhexyl phthalate and dibutyl phthalate) and T were observed among men ages 40-60 years.

References: John D. Meeker et al. Urinary Phthalate Metabolites Are Associated With Decreased Serum Testosterone in Men, Women, and Children From NHANES 2011–2012 Journal of Clinical Endocrinology Metabolism 99(11):jc20142555 · August 2014

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Obese teen boys have up to 50 percent less testosterone than lean boys

- A study by the University at Buffalo shows for the first time that obese males ages 14 to 20 have up to 50 percent less total testosterone than do non-obese males of the same age.
- **Significantly increasing their potential to be impotent and infertile as adults.**

References: Mogri, M. et al. (2013). Testosterone concentrations in young pubertal and post-pubertal obese males. *Clinical Endocrinology*, *78*(4), 593–599. doi:10.1111/cen.12018

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- Hypothyroidism
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- **Stress and/or sleep deprivation**
- Medications (opioids, anabolic steroids)

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Stress and T Levels

- **Psychosocial stress and sleep deprivation**
- Male internal medicine residents (subject), testosterone = mean **11.6** nmol/L (336ng/dl) **vs 20.6** nmol/L (594ng/dl) mean other male hospital personnel (control).
- **Psychosocial stress decreased free testosterone** after controlling for confounders like BMI, WHR, tobacco, alcohol consumption

References:
1. Singer F, Zumoff B. Subnormal serum testosterone levels in male internal medicine residents. Steroids. 1992 Feb;57(2):86-9.
2. Nilsson PM, Møller L, Solstad K. Adverse effects of psychosocial stress on gonadal function and insulin levels in middle-aged males. J Intern Med. 1995 May;237(5):479-86.

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Physical and Psychological Stress in Men in Just 5 Days

- **Urinary free cortisol increased 81%**
- **Plasma cortisol increased** from 21.7ug/100mL to 24.6
- Plasma **testosterone decreased** from 5.6ng/mL to 0.9.

References: Aakvaag, A., Bentdal, Ø., Quigstad, K., Walstad, P., Rønningen, H., & Fonnum, F. (1978). Testosterone and testosterone binding globulin (TeBG) in young men during prolonged stress. *International Journal of Andrology, 1*(1-6), 22-31.

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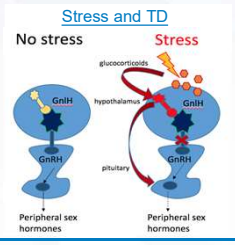
Stress Causes Central TD (Secondary)



References: Kirby ED, Geraghty AC, Ubuka, T, Bentley GE, Kaufer D. Stress increases putative gonadotropin inhibitory hormone and decreases luteinizing hormone in male rats. Proceedings of the National Academy of Sciences of the United States of America. 2009;106(27):11324-11329. doi:10.1073/pnas. 091176106.

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Sleep Loss Lowers Testosterone in Healthy Young Men

- **Cutting back on sleep drastically reduces a healthy young man's testosterone levels**, according to a study published in the June 1, 2011 issue of the *Journal of the American Medical Association (JAMA)*.
- The effects of sleep loss on testosterone levels were apparent after just one week of short sleep.
  > Five hours of sleep decreased their testosterone levels by 10 percent to 15 percent.

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- Removed testicle
- Environmental exposure
- Obesity
- Stress and/or sleep deprivation
- **Medications (opioids, anabolic steroids)**

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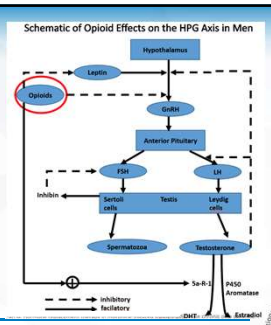
Opioids and TD

- Mechanism is inhibitory action on GnRH secretion in the hypothalamus.
- Seems dose-dependent.



References:
1. Aloisi AM, Ceccarelli I, Carlucci M, Suman A, Sindaco G, Mameli S, Paci V, Ravaioli L, Passavanti G, Bachiocco V, Pari G. Hormone replacement therapy in morphine-induced hypogonadic chronic pain patterns. Reprod Biol Endocrinol. 2011 Feb 18;9:26
2. Smith HS, Elliot JA. Opioid-induced androgen deficiency (OPIAD). Pain Physician. 2012 Jul;15(3Suppl):ES145-56. Review.

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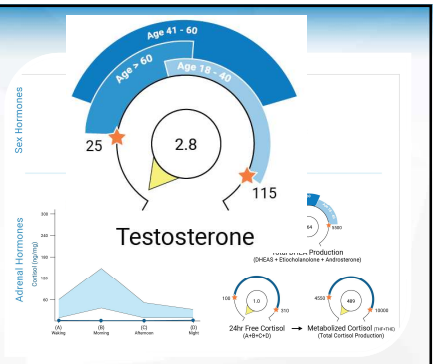
Male Patient on Tramadol with Low T



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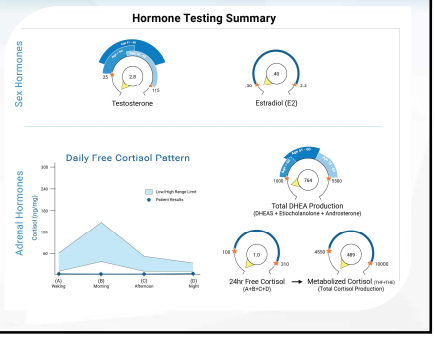
Male Patient on Tramadol with Low… Everything!



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Potential Root Causes – Less Common

- Testicular infarction
- Space occupying lesion to pituitary or hypothalamus
- Infarction affection pituitary or hypothalamus
- Decreased blood flow to the glands
- Radiation to the groin area, chemo at large

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Low T Treatment for Young Men

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Lifestyle Treatments

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Macronutrient Support for Testosterone

Goals - Eat to avoid obesity and cardiometabolic diseases:

1. Maintain high muscle mass and low visceral fat
2. Maintain excellent insulin sensitivity
3. Support mitochondrial function
4. Low glycemic
5. Lots of color
6. High in antioxidants

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Comparing Effects of Low and High-Volume Moderate-Intensity Exercise on Sexual Function and Testosterone in Obese Men

Methods: 90 abdominally obese (body mass index>27.2) sedentary (exercise ~80 minutes/week) Asian men (mean age 43.6 years, range 30-60) were prescribed a diet to reduce daily intake by ~400 kcal below calculated requirement and randomized to perform moderate-intensity exercise of LV (<150 minutes/week) or HV (200-300 minutes/week) (n=45 each) for 24 weeks. Seventy-five men (83.3%) completed the study.

Conclusions: Moderate-intensity HV aerobic exercise >200 minutes/week produces greater improvements in sexual function, testosterone, weight, WC, and fat mass than smaller exercise volume.

References: The Journal of Sexual Medicine Volume 10, Issues 7, pages 1823-1832, July 2013

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Exercise to the Rescue

Exercise → Testosterone

- A study published in 1999 examined how heavy resistance training in young men (23 – 35 years old) and older men (58 – 65 years old) affected their testosterone levels. In both the younger and older groups, there was a statistically significant increase in testosterone levels after exercise.
- Strength training in middle – aged men (44 – 48 years old) caused an increase in their levels of free testosterone.
- **Regular high-intensity exercise has been shown in multiple studies to contribute to keeping a man's testosterone at optimal levels.**

References: Izquierdo M, et al. J App Physiol 2001;90(4):1497-1507

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Mitochondrial Support – Where the First Step in T Synthesis Happens

- R-lipoic Acid
- Vitamin C
- Selenium
- B- Complex
- Magnesium, Mn, Cu
- Co Q10
- Glutathione Support
  - NAC, Sulforaphane, ALA
- Seek out and resolve chronic infections, heavy metals, autoimmunity

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Important Micronutrients to Support T

- Zinc
- Vit D
- B-complex (mitochondrial support)
- Vitamin A, C and E
- Selenium

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Multiple Studies Linking Zinc to Healthy T Levels

- There have been multiple studies on the effectiveness of zinc in treating male infertility due to low testosterone levels.
- In a study of 37 infertile men with decreased testosterone levels and associated low sperm counts: The men were given 60 mg of zinc daily for 45 to 50 days.
- In 22 patients, testosterone levels significantly increased and mean sperm count rose from 8 to 20

References:
1. Tikkiwal M, et al. Ind J Phys Pharm 1987 Jan-Mar; 31(1):30-34.
2. Takihara H, et al. Urology 1987 Jun; 29(6): 638-641.
3. Netter A, et al. Arch Androl 1981; 7(11): 69-73.

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Vitamin D3 - Many Studies Showing Adequacy of D Needed for Optimal T levels

- The male reproductive tract is a target tissue for vitamin D.
- Study: 200 healthy, overweight, nondiabetic men undergoing a weight reduction program.
- Participants received either 83 micrograms (3,332 IU) vitamin D daily for 1 year or placebo
- Compared to baseline values, a **significant increase in total testosterone, bioactive testosterone, and free testosterone levels** were observed in the vitamin D supplemented group.

References: Pilz S, Frisch S, Koertke H, et al. Effect of Vitamin D Supplementation on Testosterone Levels in Men. Hormone and Metabolic Research. 2010;43(03):223-225.

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Selenium Protective Effect on Testes and Serum T Levels In Cd Exposure in Chickens

- **Exposure to Cd significantly lowered** SOD and GPx activity, Se content in the testicular tissue, and **serum testosterone levels.**
- Concurrent treatment with Se reduced the Cd-induced histopathological changes in the testis, oxidative stress, endocrine disorder and apoptosis, suggesting that **the toxic effects of cadmium on the testes is ameliorated by Se.**
- Se supplementation also modified the distribution of Cd in the testis.
- Human studies ??

References:
1. Li J, Gao R, Li S, Wang J, Tang Z, Xu S. Testicular toxicity induced by dietary cadmium in cocks and ameliorative effect by selenium. Biometals: An International Journal On The Role Of Metal Ions In Biology, Biochemistry, And Medicine. August 2010;23(4):695-705.
2. Ren X, Wang G, Cai Y, et al. The protection of selenium on cadmium-induced inhibition of spermatogenesis via activating testosterone synthesis in mice. Food And Chemical Toxicology: An International Journal Published For The British Industrial Biological Research Association. October 2012;50(10):3521-3529

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Medical Intervention for Young Men

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Testosterone Sparing Options

- Botanicals
- HCG
- Clomiphene Citrate (Clomid)

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Botanicals Shown to Increase T Levels

- Tribulus?
- Maca?
- Fenugreek
- Mucuna
- Ashwagandha
- Black Seed

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Materials and Methods

- A focused literature search was conducted to include studies published in Cochrane, Pubmed, and Web of Science databases between the years 2002 and 2018

Botanicals and Testosterone

Heitor O. Santos et al. Beyond tribulus (*Tribulus terrestris* L.): The effects of phytotherapics on testosterone, sperm and prostate parameters. Journal of Ethnopharmacology Volume 235, 10 May 2019, Pages 392-405

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Phytonutrients: Testosterone, Sperm and Prostate Health

Results

The use of tribulus and maca (*Lepidium* meyenii Walp, Brassicaceae) were not scientifically supported to improve serum T levels in men. Moderate evidence supports the use of long Jack (*Eurycoma longifolia* Jack, Simaroubaceae), mucuna (*Mucuna pruriens* (L.) DC., Fabaceae), ashwagandha (*Withania somnifera* (L.) Dunal, Solanaceae), fenugreek (*Trigonella* foenum-graceum L., Fabaceae), and black seeds (*Nigella sativa* L., Ranunculaceae) to increase total T and improve seminal parameters. The use of mucuna was supported for patients with oligozoospermia to improve sperm parameters, with an increase of 83.3 million/mL observed after use of 5000 mg/d of powdered mucuna seed over a 12-week period.

Evidence supporting the use of saw palmetto (*Serenoa repens*, (W.Bartram) Small, Arecaceae) to improve prostate health remains equivocal; whereas, evidence supporting the use of *Pygeum africanum* Hook.f., Rosaceae, *Urtica dioica* L., Urticaceae, beta-sitosterols, pollen extract, onion, garlic, and tomato, appears favorable and promising.

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Ashwagandha and Mucuna to Raise T

- Data suggests an increase in total serum T in humans with the use of 5000 mg/d of powdered mucuna seed (Long Jack) and ashwagandha root (151 and 143 ng/dL, respectively) over a 12-week period

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Botanicals That Raise Serum Testosterone

Conclusion

Scientific evidence supports the use of mucuna and ashwagandha as phytotherapics for improving serum T concentrations and semen parameters. Despite inconclusive evidence for use of tribulus as a T booster, it may provide advantageous effects on sperm parameters in men with idiopathic infertility.

Nutraceutical strategies and some phytotherapies may also be effective to promote prostate health. Popular foodstuffs (onion, garlic, and tomato), nutraceutical agents (pollen extract and beta-sitosterols), and herbal medicines (*Pygeum africanum* and *Urtica dioica*) are rational approaches.

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Medical Intervention Preserving Fertility

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Testosterone Deficiency in Post-Pubescent Males Desiring Fertility

- Testosterone required for maintenance of established spermatogenesis as well as restoration or spermatogenesis if disrupted for any reason.
- FSH is necessary for initiating and maintaining spermatogenesis in addition to achieving full testicular volume. (Sertoli and germ cell proliferation)
- Giving FSH or LH (hCG) alone will increase sperm counts but not to normal.

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Testosterone Deficiency in Post-Pubescent Males During Fertility – Need Both FSH and LH Effects

- Studies show need FSH 150IU + LH (hCG) 1500IU three times a week sub-Q injection to initiate and maintain spermatogenesis.
- Testosterone levels will rise with LH (hCG) given sub-Q alone.
- Both FSH and LH (hCG) effects on the Sertoli cells required for complete testicular development.
- Studies show that giving pure FSH and Testosterone will not induce quantitatively normal spermatogenesis-LH (hCG) effects needed to get max sperm counts.

References: Ramasamy R, Armstrong J, Lipshultz L. Preserving fertility in the hypogonadal patient: an update. Asian Journal of Andrology. March 2015;17(2):197-200

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Medical Intervention

- TRT (discussed later in aging male conversation)
- HCG
- Clomid

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Options for Young Men

- Testosterone Replacement Therapy (TRT)
  - Will cause testicular atrophy
  - Will suppress endogenous production
- Testosterone Sparing Options
  - Must have functional gonads
  - Increase endogenous T production
  - No testicular atrophy

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Testosterone Sparing for Young Men

- HCG – LH analog
- Clomiphene Citrate (selective estrogen receptor modulator – SERM)

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Using HCG to Increase Testosterone Production

- Pulsed doses of HCG 1200-3000IU s.c. divided evenly over a week for 2-3 months followed by a holiday x 1 month, can be effective with or without additional testosterone therapy.
- Also available as a sublingual troche
- Monitoring side effects, DRE, LUTS, watching PSA, CBC, ALT, Testosterone, Estrogen, and DHT are still very important.
- Expensive and off-label for men

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Citations for Previous Slides

- G. Schaison et al. 1993. Failure of combined follicle-stimulating hormone-testosterone administration to initiate and/or maintain spermatogenesis in men with hypogonadotropic hypogonadism. *The Journal of Clinical Endocrinology & Metabolism*, Volume 77, Issue 6, 1 December 1993, pages 1545-1549, https://doi.org/10.1210/jcem.77.6.8263139
- J. Rajkanna et al. 2016 January 7. Successful Fertility Treatment With Gondatrohphin Therapy for Male Hypogonadotrophic Hypogonadism. Endocinol Diabetes Metab Case Rep. 2016; 2016: 150124. Doi: 10.1530/EDM-15-0124
- R. A. Ray et at. 2013. Male hypogonadism: an extended classification based on a developmental, endocrine physiology-based approach. Andrology, 2013, 1, 3-16. doi: 10.1111/j.2047-2927.2012.00008.x

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Clomid to Increase Testosterone Production

- **Clomiphene Citrate**
  - 25mg and 50mg tablets start with 1 po q day MWF and can build to 50mg a day as needed.
  - Often take drug holidays.
  - Works as a SERM to block E2 negative feedback on hypothalamic receptors – effectively increasing LH/FSH.

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Clomid to Increase Testosterone Production

- Advantages:
  - No central LH/FSH suppression
  - Fertility maintained and no testicular atrophy
  - Less expensive and easier to use than hCG
  - Can be used alone or combined with hCG to raise sperm counts and serum T
- Disadvantages:
  - Off label for androgen support but on label for induction of spermatogenesis
  - Rare gastrointestinal distress, dizziness, hair loss, gynecomastia, and minimal weight gain
  - 1.5% risk of visual disturbances which resolve upon drug cessation

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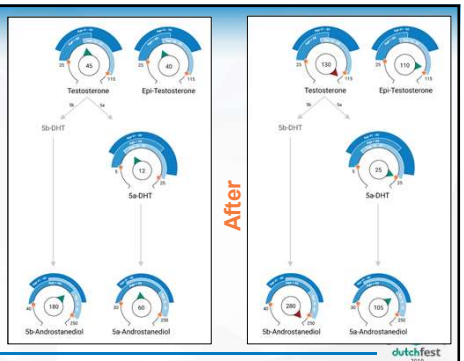
Clomid to Increase T

Serum T increased from 325 to 881ng/dL on a loading dose (50mg/day)



71

Citations for Clomiphene Citrate and hCG

- Ahmad Shabsigh et al. Clomiphene Citrate Effects on Testosterone/Estrogen Ratio in Male Hypogonadism. Journal of Sexual Medicine. 2(5):716-21. October 2005
- Joshua D Ring et al. Current medical management of endocrine-related male infertility. Asian J Androl. 20106 May-Jun; 18(3):357-363
- Pranav Dadhich et al, Testosterone versus clomiphene citrate in managing symptoms of hypogonadism in men. Indian J Urol. 2017 Jul-Sep; 33(3):236-240
- Kaminetsky J et al. Oral enclomiphene citrate stimulates the endogenous production of testosterone and sperm counts in men with low testosterone: comparison with testosterone gel. J of Sex Med. 2013 Jun;10(6):1628-35
- Mohamad Habous et al. Clomiphene citrate and human chorionic gonadotropin are both effective in restoring testosterone in hypogonadism: a short-course randomized study. Andrology. November 2018 Volume122, Issue 5 Pages 889-897
- V. Madhusoodanan et al. 233 Human Chorionic Gonadotropin (hCG) Monotherapy for the Treatment of Symptoms of Hypogonadism in Men with Total Testosterone > 300ng/Dl April 2019 Volume 16, Issue 4 Supplement1, Page S113

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Lab Assessment: Low T in Aging Men

73

What Do We Know About T and Aging

- After age 25, in some men, T decreases by 0.3-1.4%/year
- After age 40, observational studies demonstrate that T:
  - Decreases by 1.0-1.6%/year
  - SHBG increases by ~ 1.3%/year
    - Greater decrease in Free T bioavailable T, as opposed to total T, because of increasing SHBG
  - Free T decreases by ~ 2.8%/year

References: Erenpreiss J, et al. *Aging Male*. 2019. DOI: 10.1080/13685538.2019.1621832

74

TD Prevalence

- In the US: 4 studies: prevalence ranging from 6% to 30%
- European Male Aging Study: 23.3% w/o SS, 2.1% w/ SS
  - Criteria: 3 SS consistent with TD + total serum T < 320ng/dL + low free T
    - SS: decreased libido, decreased AM erections, erectile dysfunction
- Asian countries: prevalence ranges from 9.5% to 30%
- Australia and South American countries: prevalence ranging from 14% to 43% in men with obesity, DM, or metabolic syndrome

References: Morgentaler A, et al. *Mayo Clin Proc*. 2016; 91(7):881-896.

75

KEY POINTS

- TD is common
- Age is not a risk factor – Aging males can have healthy T levels, young men can have TD
- Diagnosis not just a lab test – assess entire clinical picture
- Regardless of age, look for clinical associations and root causes

76

Lab Options I Do NOT Use

- Saliva and bloodspot testing can be used but are less reliable and not well standardized
- Serum "Free Androgen Index" – Calculation based on T and SHBG
  - Statistical analysis shows this to be a poor predictor of free T, bioavailable T, and TD.
  - Endocrine Society says not a helpful measure for Free T or Bioavailable T

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Assessing Testosterone (serum T)

78

Initial Diagnostic Lab Testing for TD
(Use Serum)

The "normal range" for serum is generally 300 to 1,000 ng/dL

- Check between 7-10 AM if < 45 years old
- Must confirm with a second draw on a separate day
- Best if 8 hours since last full meal, 24 hours since sexual activity or stressors (physical/mental)
- Consider Root Causes of transitory low T (acute illness, medications)

300ng/dl is the conventional line in the sand. Repeat and Confirm!

References: Paduch D, Brannigan R, Fuchs E, Kim E, Marmar J, Sandlow J. The laboratory diagnosis of testosterone deficiency. Urology [serial online]. May 2014;83(5):980-988

79

Initial Diagnostic Serum Testing for TD

Step 1 – Test and Confirm Low Total T

- Fasting Total testosterone in morning as near to 8 AM as possible (prior to 10 AM)

If Total T is low or borderline low *confirm on another day*.

- If you suspect a condition that can alter SHBG is present (liver disease, IR, obesity, high E2) draw calculated Free T and SHBG levels with step 2. I do this on everybody.

References: Bhasin, S et al. J Clin Endocrinal Metab 2006; 91: 1995-2010

80

Diagnostic Serum Testing for TD – Confirming the Diagnosis

Step 2 – Can I trust the total T and why is T low?

- Confirm low T and include other labs
- Prolactin-if up, will need MRI of sella for adenoma
- If LH elevated think primary/compensated causes

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Alternate Lab Options I Use

- **Testosterone**
- SHBG
- LH, FSH
- PSA
- Estradiol, DHEA-S, DHT (ADG)
- Prolactin, Ferritin
- CBC with Differential

I often test only T initially and test the rest when confirming low T

82

Hormone Trends in Males With Aging

- **Decreases**:
  - Testosterone and DHEA around age 30y
  - Progesterone around age 50y
  - Pregnenolone around age 30y
- **Increases**:
  - SHBG
  - PSA and Prostate Volume
  - E2 around age 50y
  - LH, FSH (primary & compensated TD
  - Prolactin

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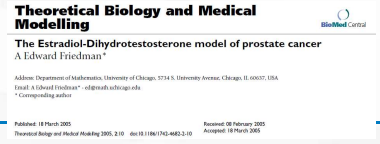
Estrogen Dominance In Males

- As men age >50, prostate levels of estradiol gradually rise, and levels of progesterone and testosterone decline. The decline in testosterone and progesterone levels is greater than the rise of estradiol.
- Estradiol and DHT are synergistic in creating prostate problems.



Theoretical Biology and Medical Modelling

BioMed Central

The Estradiol-Dihydrotestosterone model of prostate cancer

A Edward Friedman*

Address: Department of Mathematics, University of Chicago, 5734 S. University Avenue, Chicago, IL 60637, USA

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* Corresponding author

Published: 18 March 2005

Theoretical Biology and Medical Modelling 2005, 2:10 doi:10.1186/1742-4682-2-10

Received: 08 February 2005

Accepted: 18 March 2005

84

What Upregulates Aromatase?

- Excess alcohol
- Zinc deficiency
- Insulin resistance
- Inflammation PGE2
- Obesity (central)
- Stress
- Cortisol
- Leptin
- Aging
- Gonadotropins

85

References on Estrogen Dominance

- Matsuda T, Abe H, Suda K. [Relation between benign prostatic hyperplasia and obesity and estrogen]. Rinsho Byori. The Japanese Journal Of Clinical Pathology. April 2004;52(4):291-294.
- Aggarwal S, Thareja S, Verma A, Bhardwaj TR, Kumar M. An overview on 5alpha-reductase inhibitors. Steroids. 2010 Feb;75(2):109-53. doi: 10.1016/j.steroids.2009.10.005.
- Cabeza M, Heuze I, Bratoeff E, Murillo E, Ramirez E, Lira A. New progesterone esters as 5alpha-reductase inhibitors. Chem Pharm Bull (Tokyo). 2001 Sep;49(9):1081-4.

86

TD: Diagnosis

- TD diagnosis should include the entire clinical picture aided by laboratory testing
- Rigid reliance on serum total testosterone has limitations
  - No study has documented a single testosterone threshold that reliably distinguishes those men with SS 2^0 to TD, from those men who do not

References: Morgentaler A, et al. *Mayo Clin Proc.* 2016; 91(7):881-896.

87

Root Cause Check Before Considering TRT

88

Potential Root Causes

- Hypothyroidism
- TBI (male patients in violent sports are at risk)
- Zinc deficiency (gut issues, malabsorption)
- Regular alcohol or THC use
- Removed testicle
- Environmental exposure
- Obesity
- Stress and/or sleep deprivation
- Medications (opioids, anabolic steroids)

89

Root Causes – Specific to Aging Males

- Age
- Diabetes
- Elevated SHBG
- Increased conversion to estrogen (aromatization)
- Radiation (to the groin area) or chemotherapy

90

KEY POINTS

- TD is common
- Older men can have healthy levels, Young men can have TD
- Diagnosis not just a lab test – assess entire clinical picture
- Regardless of age, look for clinical associations and root causes
- **Low T levels are associated with comorbidities such as obesity, IR/DM, metabolic syndrome (Met-S), sleep apnea, and cardiovascular disease**
- **TD predicts development of DM, Met-S, osteoporosis, etc.**

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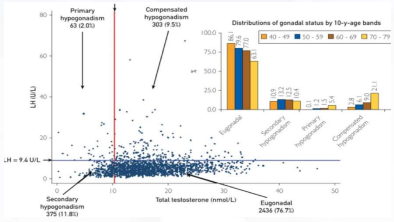
Male Subgroups by Gonadal Status and Decade of Age



References: Khera M, Broderick GA, Carson CC, et al. Adult-Onset Hypogonadism. *Mayo Clinic Proceedings*. 2016;91(7):908-926. doi:10.1016/j.mayocp.2016.04.022

92

Comorbidities and TD

Inflammation is the key to many testosterone deficiency comorbidities.

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TD Comorbidities Improved by TRT

- Inflammation
- Decreased Libido / Erectile Dysfunction
- Loss of Bone Mineral Density and/or Muscle Mass
- Metabolic Dysregulation: Obesity/IR/DM/Met-S
- Cardiovascular Disease (CVD)

TD Comorbidities with Unclear Relationship to TRT

- Cognitive Decline
- Prostate Health

TD Comorbidity NOT Improved by TRT

- Obstructive Sleep Apnea (OSA)

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TD and Inflammation

- Testosterone is an immune modulator

Low T increases inflammation
TRT decreases inflammation

- Androgens (and estrogens) regulate the function of:
  - Macrophages, monocytes, neutrophils, eosinophils, mast cells, etc
  - Inflammatory cytokine expression including, but not limited to: TNF-α, IL-1β, IL-6, and CRP

References: Traish A, et al. *J Clin Med.* 2018, 7, 549: 1-33. DOI: 10.3390/jcm7120549.

95

TD and Inflammation

- T is an immune modulator
  - Neutrophils, mast cells, B-cells, and T-cells all express androgen receptors (AR)
  - Androgens (and estrogens) regulate the function of:
    - Macrophages, monocytes, neutrophils, eosinophils, mast cells, etc
    - Inflammatory cytokine expression including, but not limited to: TNF-α, IL-1β, IL-6, and CRP

TRT decreases inflammation and related cytokines

References: Traish A, et al. *J Clin Med.* 2018, 7, 549: 1-33. DOI: 10.3390/jcm7120549.

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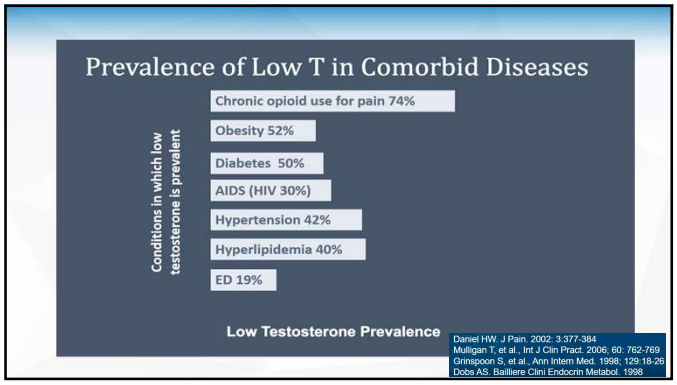
TD, Inflammation, and Clinical Associations

- **Metabolic Dysregulation**
  - Obesity
  - IR/DM
  - Met-S
- **Obstructive sleep apnea**
- **Cardiovascular disease**
- **Cognitive impairment/AD**
- Autoimmune diseases
  - Psoriasis
  - Crohn's
  - Rheumatoid arthritis
- **Prostate disease**

References: Traish A, et al. *J Clin Med*. 2018, 7, 549: 1-33. DOI: 10.3390/jcm7120549.

97



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TD Comorbidities Improved by TRT

- Inflammation
- **Decreased Libido / Erectile Dysfunction**
- Loss of Bone Mineral Density and/or Muscle Mass
- Metabolic Dysregulation: Obesity/IR/DM/Met-S
- Cardiovascular Disease (CVD)

99

Testosterone and Libido in Men

It has been established in the medical literature that testosterone sufficiency optimizes male libido…

1. Rizk PJ **et al. Testosterone therapy improves erectile function and libido in hypogonadal men.** Curr Opin Urol. 2017 Nov;27(6):511-515.
2. Thomas G. Travison et al. **The Relationship between Libido and Testosterone Levels in Aging Men.** *The Journal of Clinical Endocrinology & Metabolism*, Volume 91, Issue 7, 1 July 2006, Pages 2509–2513
3. Morley JE 2003 Testosterone and behavior. *Clin Geriatr Med* 19:605–616
4. Matsumoto AM 2002 Andropause: clinical implications of the decline in serum testosterone levels with aging in men. *J Gerontol Med Sci* 57:M76–M99

100

The Role of Testosterone in Erectile Function

SUMMARY:

The available literature supports a role for TRT in men with low testosterone levels, erectile dysfunction, and low libido, with symptomatic improvement in these men.

References: Rizk PJ **et al. Testosterone therapy improves erectile function and libido in hypogonadal men.** Curr Opin Urol. 2017 Nov;27(6):511-515

101

Nitric Oxide and Testosterone Both Needed for Erectile Function

- The nitric oxide (NO) pathway is critical for initiation and maintenance of erective function.
- NO and NO synthase in the corpus cavernosum is regulated by androgens.
- NOS activation is markedly decreased in castrated animals. Testosterone restores the erectile response and normalized NOS protein expression and activity.

References: Li R, Meng X, Rao K, et al. Testosterone improves erectile function through inhibition of reactive oxygen species generation in castrated rats. PeerJ. May 3, 2016;4:e2000

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TD Comorbidities Improved by TRT

- Inflammation
- Decreased Libido / Erectile Dysfunction
- **Loss of Bone Mineral Density and/or Muscle Mass**
- Metabolic Dysregulation: Obesity/IR/DM/Met-S
- Cardiovascular Disease (CVD)

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Journal of Endocrinology and Metabolism

403 healthy men aged 73-to-94 years, were examined relative to decreases in muscle strength, bone mass, and body composition.

Findings:

Muscle strength and bone mass were at optimal levels in men with the highest levels of free testosterone, leading the authors to state that "a number of clinical problems present in older men may be related to androgen [testosterone] deficiency, including reduced muscle mass, changes in body composition, and loss of BMD [bone mass density]."

References: van den Beld A, de Jong F, Grobbee D, Pols H, Lamberts S. Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men. The Journal Of Clinical Endocrinology And Metabolism [serial online]. September 2000;85(9):3276-3282.

104

Bigger Muscles & Stronger Bones

Building muscle mass and bone density while reducing abdominal fat are well-established improvements in body composition observed in response to testosterone therapy (assuming sufficient growth hormone present).

References:
1. Isidori AM, et al. Clin Endocrinol (Oxf). 2005 Sep;63(3):280-93.
2. Moretti C, et al. J Endocrinol Invest. 2005;28(3 Suppl):56-64
3. Wang C, et al. J Clin Endocrinol Metab. 2004May;89(5):2085-98

105

Testosterone & Growth Hormone Work Together

- Roles of GH
  - Building and maintaining lean muscle mass
  - Lipolysis and fat reduction
  - Improved bone mass-type 1 collagen, osteocalcin
  - Less atherosclerosis (CIMT data)
  - Favorable lipid profiles
  - IGF-1 and GH are not the same thing and have unique roles
  - In different body tissues from one another

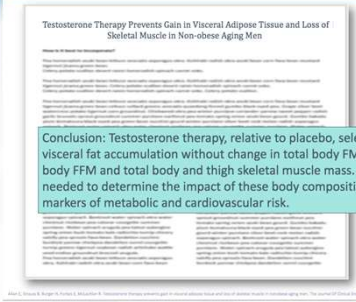
106

Restoring "T" for Lean Muscle

- TRT for 10 men, 60–78 years in age (double-blind trial)
- TRT improved fat-free mass, exercise endurance time and balance

References: 1. Brill K, Weltman A, Veldhuis J, et al. Single and combined effects of growth hormone and testosterone administration measures of body composition, physical performance, mood, sexual function, bone turnover, and muscle gene expression in healthy older men. The Journal of Clinical Endocrinology And Metabolism. December 2002;87:5649-5657.

107


Testosterone Therapy Prevents Gain in Visceral Adipose Tissue and Loss of Skeletal Muscle in Non-obese Aging Men

Conclusion: Testosterone therapy, relative to placebo, selectively lessened visceral fat accumulation without change in total body FM and increased total body FFM and total body and thigh skeletal muscle mass. Further studies are needed to determine the impact of these body compositional changes on markers of metabolic and cardiovascular risk.

108

T as a Bone Builder

109

T-Trials Showed Clear Benefits to Bone by Replacing Testosterone in Men Over 65 That Were Low-2017

In the Bone Trial, testosterone increased volumetric bone mineral density and estimated strength of the spine and hip.

References: P.J. Snyder et al. 2018. Lessons From The Testosterone Trials. Endocr Rev. 2018 Mar 7. doi: 10.1210/er.2017-00234. (Epub ahead of print)

110

Testosterone and Structure

- Testosterone supplementation can also **help reverse sarcopenia and osteoporosis.**
- Supplemental testosterone has been shown to **increase bone mass of the lumbar spine in elderly men.**
- A 1995 study showed testosterone given men aged 64-to-69 who had low testosterone levels caused a **measurable increase in skeletal muscle protein synthesis and strength.**

111

References on Structure and T

1. Snyder P, Peachey H, Strom B, et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. The Journal Of Clinical Endocrinology And Metabolism [serial online]. June 1999;84(6):1966-1972.
2. Urban R, Bodenburg Y, Ferrando A, et al. Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. The American Journal Of Physiology [serial online]. November 1995;269(5 Pt 1):E820-E826.
3. Fitts R, Peters J, Dillon E, Durham W, Sheffield-Moore M, Urban R. Weekly versus monthly testosterone administration on fast and slow skeletal muscle fibers in older adult males. The Journal Of Clinical Endocrinology And Metabolism. February 2015;100(2):E223-E231.

112

TD Comorbidities Improved by TRT

- Inflammation
- Decreased Libido / Erectile Dysfunction
- Loss of Bone Mineral Density and/or Muscle Mass
- **Metabolic Dysregulation: Obesity / IR / DM / Met-S**
- Cardiovascular Disease (CVD)

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TD and Metabolic Dysregulation

Obesity

- BMI>30, TD 3X as likely
- BMI >35, 2/3 have TD (Normal weight, only 1/6)

Visceral Adiposity

- T aromatization to E
  - Leads to increased E levels which, via negative feedback, inhibits the HPG axis, decreasing T
- A highly active endocrine organ
  - Secretes inflammatory cytokines, procoagulant substances, stimulates RAA system

References:
1. Wu F, et al. *J Clin Endocrinol Metab.* 2008; 93(7): 2737-2745.
2. Mah PM, Wittert GA. *Mol Cell Endocrinol.* 2010; 316(2): 180-186.
3. Dudek P, et al. *Menopause Rev.* 2017; 16(2): 66-69.

114

TD and Metabolic Dysregulation

- Obesity, Intestinal Permeability, Metabolic Endotoxemia (Important inflammatory Trigger for low T)
  - Obesity, with its subsequent inflammation, increases intestinal permeability via breakdown of the mucosal integrity
    - LPS translocates into the circulation increasing inflammatory cytokines IL-1β, TNFα, IL-6, as well as CRP

References: Tremellen K. *Basic Clin Androl.* 2016; 26(7).

115

TD and Metabolic Dysregulation

- Obesity, Intestinal Permeability, Metabolic Endotoxemia (Important inflammatory Trigger for low T)
  - The resulting chronic low-grade inflammation/endotoxemia impairs testicular Leydig and Sertoli cell steroidogenesis leading to low T, possible fertility issues, and persistent immune dysregulation

References: Tremellen K. *Basic Clin Androl.* 2016; 26(7).

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TD and Metabolic Dysregulation: Met-S

- Low T may be among the earliest detectable signs that a man is undergoing the bodily changes that **will later become apparent as obesity and the metabolic syndrome**
  - **Low T impairs insulin signaling**
  - **Low T increases inflammatory markers**

References: Traish A, et al. *J Clin Med.* 2018, 7, 549: 1-33. DOI: 10.3390/jcm7120549.

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TD and Metabolic Dysregulation

- Bidirectional relationship between IR states and TD
  - Numerous studies showed a close association between obesity, metabolic syndrome, and TD
  - Recip[illegible]k of develo[illegible]
    - Clo[illegible]
    - Total T depends on SHBG levels and IR decreases SHBG
    - Therefore, metabolic syndrome worsens low T, and low T worsens metabolic syndrome

A Viscous Cycle

References: Ebrahimi F, Christ-Crain M. *Swiss Med Wkly*. 2016; 146: w14283.

118

TD and Metabolic Dysregulation: Met-S

- Met-S, similar to obesity, is a chronic inflammatory syndrome
  - Increased visceral adiposity is associated with increased pro-inflammatory cytokines that inhibit the HPG axis leading to TD
- (3) Met-S components designated as key in exacerbating age-related decrease in T levels
  - High TG (> 150mg/dL), elevated FBS (>110mg/dL)/DM, and obesity (BMI ≥ 30) each had a relevant association with low T

References: Surampudi P, et al. *Int J Endocrinol*. 2012; 1-21.
Ebrahimi F, Christ-Crain M. *Swiss Med Wkly*. 2016; 146: w14283.

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TD Comorbidities Improved by TRT

- Inflammation
- Decreased Libido / Erectile Dysfunction
- Loss of Bone Mineral Density and/or Muscle Mass
- Metabolic Dysregulation: Obesity/IR/DM/Met-S
- **Cardiovascular Disease (CVD)**

120

TD, Inflammation, and CVD

- The evidence does not support increased CVD risk with TRT
- The evidence does support low T levels are associated with increased CVD risk
- Higher T levels reduce CVD risk, improve CVD risk factors, and reduce mortality in T-deficient men who get treated with TRT - Results from more than 100 studies

References: Morgentaler A, et al. *Mayo Clin Proc.* 2016; 91(7):881-896.

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TD, Inflammation, and CVD

- Observational studies revealed with low T, there is increased:
  - Mortality, atherosclerosis, coronary disease, CIMT, fat mass, and dysglycemia
- Observational studies reported ~ 50% mortality reduction with TRT (to normal physiologic levels) in T deficient men

References: Morgentaler A, et al. *Mayo Clin Proc.* 2016; 91(7):881-896.

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Key Points

- Obesity, IR/DM, Met-S, OSA, and CVD are all chronic inflammatory states that are highly prevalent and associated with significant morbidity and mortality, including CV mortality – TD common in all of these
- TD, independent of the above, is associated with an adverse CVD risk profile and increased atherosclerosis

Testosterone therapy improves outcomes

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TD Comorbidities with Unclear Relationship to TRT

- **Cognitive Decline**
- Prostate Health

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TD, Inflammation, and Cognition

- T hypothesized to be important for cognition in men and supported by studies
  - Influences neurobiological processes involved with cognitive aging and AD
  - T has been found to:
    - Delay neuronal apoptosis and accelerate rate of regeneration
    - Modulate oxidative stress induced neuronal damage
    - Exert anti-inflammatory effects
    - Reduce β-amyloid peptide levels

References: LV W, et al. *Mol Neurobiol*. 2016; 53: 2679-2684.

125

TD, Inflammation, and Cognition

- Low T is significantly associated with increased AD risk and worsening cognition in elderly men
- TRT thus far, does not improve cognitive function
  - Testosterone Trials (7 total trials)
    - Among men >65 with low T (< 275ng/dL) and age-associated memory impairment, **TRT for 1 year compared with placebo was <u>not</u> associated with improved memory or other cognitive functions**

References:
1. LV W, et al. *Mol Neurobiol*. 2016; 53: 2679-2684.
2. Resnick S, et al. *JAMA*. 2017; 317(7): 717-727.
3. Surampudi P, et al. *Int J Endocrinol*. 2012; 1-21.

126

TD Comorbidities with Unclear Relationship to TRT

- Cognitive Decline
- **Prostate Health**

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Testosterone and Prostate Health

- Testosterone and its 5α-reduced active form (5α-DHT) are both required for the development and maintenance of a functioning prostate gland
- The prostate's androgen receptor (AR) binds both DHT and testosterone, but has a higher affinity for DHT

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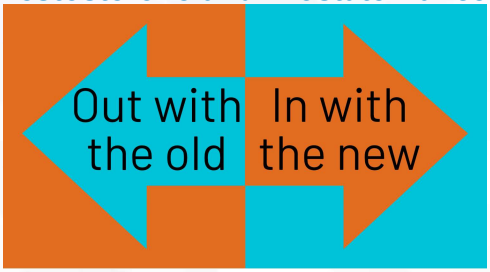
Testosterone and Prostate Cancer



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Testosterone and Prostate Cancer

- The Saturation Model: what the evidence shows
  - The prostate is androgen dependent for optimal growth and development
  - There is a limited ability for androgens to stimulate prostatic growth
  - Maximum androgen driven growth is achieved at lower serum T levels
- This model explains the paradoxical observations that the prostate is:
  - "Exquisitely sensitive" to serum T levels at low concentrations
  - But is indifferent to changes at higher concentrations

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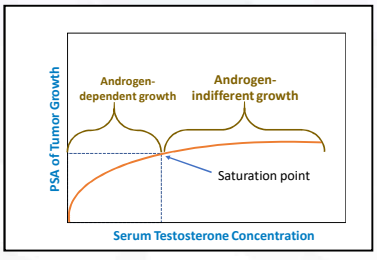
Testosterone and Prostate Cancer

- Saturation Model Mechanisms
  - Maximum binding of androgens to the AR
    - Androgens have a finite ability to bind to the AR
    - In clinical practice, the saturation point is ~ 250ng/dL (subject to interindividual variation)
      - Dramatic changes in PSA when serum T levels are manipulated below or above 250ng/dL
      - Minimal or no PSA changes when supraphysiologic levels are given to men with normal T
  - Local regulatory mechanisms
    - Prostate maintains a homeostatic microenvironment
      - Intraprostatic androgen levels remain constant despite increases in T

131

Testosterone and Prostate Cancer



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Testosterone and Prostate Cancer

- Saturation Model Implications
  - Serum T levels below the saturation point (~ < 250ng/dL) will reduce PSA, decrease prostate volume in men with benign or malignant tissue
  - Raising serum T levels from anywhere below the saturation point will increase PSA and tissue growth
  - Increasing T above ~ 250ng/dL results in limited or no growth
  - Men with T levels way below the saturation point, treated with TRT will experience the greatest increase in PSA compared to men with T levels just below the saturation point

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Testosterone, Prostate Cancer: The Data

- Endogenous T
  - > 20 population based longitudinal studies show no relationship between PCa, serum T, and/or other androgens
- TRT and PCa risk
  - No prospective, randomized, controlled trials with adequate population sizes and duration have been performed to answer the TRT and PCa risk question
  - To date, all the evidence fails to document an increased risk with TRT
  - Modern data offers strong evidence that serum T levels are unrelated to PCa risk

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Testosterone, Prostate Cancer: The Data

- Low serum T and PCa risk
  - Studies have suggested that low T increases (+) prostate biopsy risk
  - Studies report an association of low T (< 300ng/dL) with high-grade and PCa stage at presentation
  - Men with T levels in lowest tercile had ~ double the risk of biopsy (+) PCa compared with less severe TD
  - Low T levels associated with a poor prognosis

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Testosterone and Prostate Cancer

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Testosterone, Prostate Cancer: The Data

- Th… …ose that ar…
- Th…
  - …ectomy

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Testosterone, Prostate Cancer: The Data

- More risky group are men treated with XRT or brachytherapy
  - Possibility exists of residual *in situ* PCa
  - Men have low, but detectable PSA, with fluctuating levels
  - If PSA rises, the knee-jerk response is: it's the TRT
- The high risk groups include men with advanced, recurrent, or metastatic disease

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Slide 136

HD4 Not exactly sure what to do with thses slides...
Heather Daniel, 8/29/2019

Testosterone, Prostate Cancer: The Data

- More risky grou… r brachytherapy
  - Possibility exist…
  - Men have low, … g levels
  - If PSA rises, th… T
- The high risk gr… ced, recurrent, or metastatic disea…

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Medical Legal –Informed Consent

Prostate Health:
A Medical Consideration

- Informed consent needed before you treat with ANY steroidal hormone

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Testosterone, Prostate Cancer, & Estrogen

- Estrogen and Prostate Cancer
  - Estrogen's role in PCa is complicated
  - On one hand, estrogen and phytoestrogens are used to prevent/treat prostate cancer
  - On the other hand, estrogen has been implicated in prostate cancer development and progression
  - Serum levels may not correlate, prostate converts T to E via aromatase
    - Aromatase activity 30-fold higher in prostate cancer metastatic tissue than in primary tumor

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Testosterone, Prostate Cancer, & Estrogen

- Estrogen and Prostate Cancer
  - Prostate expresses both phase I (CYP1A1 and CYP1B1) and phase II (Catechol-O-Methyl transferase) detoxification enzymes
  - Estrogens are capable of upregulating CYP1B1's expression
  - CYP1B1 is also differently expressed in each prostate zones
    - Higher expression levels in the more cancer-prone peripheral zone
    - Important to ensure adequate methylation and rapid excretion

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Prostate Cancer: Other Root Causes

- Estrogen, Prolactin, and Prostate Cancer
  - Chronic estrogen exposure increases circulating prolactin
  - In prostate epithelial cells, autocrine prolactin activates Stat5 an important survivability factor for prostate cancer cells associated with hormone resistance, higher histological grade, and earlier recurrence
- Chronic inflammation associated with prostate cancer
  - Increased oxidative stress, free radical formation, and DNA damage
  - Increased PCa incidence in men with prostatitis

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DUTCH and Prostate Risk

- Testosterone
- DHT and Estradiol synergistically create prostate problems
- Estrogen metabolites (4-OH estrogens, methylation) play a role
- Also monitor melatonin, 8-OHdG, pyroglutamate, cortisol

- DUTCH is a good compliment to serum testing for men's health

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References for Previous Slides

- Khera M, et al. *Eur Urol*. 2014; 65(1): 115-23.
- Morgentaler A, Conners WP III. *Asian J Androl*. 2015; 17(2): 206-211.
- Morgentaler A, et al. *Mayo Clin Proc*. 2016; 91(7):881-896.
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- Santella C, et al. *Am J Epidemiol*. 2019; kwz138. doi: 10.1093/ajekwz138
- Nelles J, et al. *Expert Rev Endocrinol Metab*. 2011; 6(3): 437-451.

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TD Comorbidity NOT Improved by TRT

- Obstructive Sleep Apnea (OSA)

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TD, Inflammation, and OSA

- OSA, another chronic inflammatory state
  - OSA directly inhibits HPG function
    - Serum T follows the same circadian rhythm as cortisol
    - T begins to rise upon falling asleep, peaks simultaneously with first REM episode, and remains at that level until awakening
  - Sleep fragmentation with the intermittent hypoxic episodes disrupts T's circadian rhythm causing attenuation of T's nocturnal increase
  - Obesity common with OSA and associated with increased severity

References:
1. Kim SD, Cho KS. *World J Men's Health*. 2019; 37(1): 12-18.
2. Surampudi P, et al. *Int J Endocrinol*. 2012; 1-21.
3. Traish A, et al. *J Clin Med*. 2018, 7, 549: 1-33. DOI: 10.3390/jcm7120549

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TD, Inflammation, and OSA

- Testosterone Therapy **⚠CAUTION**
  - No convincing evidence to date that TRT aggravates OSA
  - However, untreated OSA contraindication to TRT
  - Have a high clinical suspicion

Kim SD, Cho KS. *World J Men's Health.* 2019; 37(1): 12-18.

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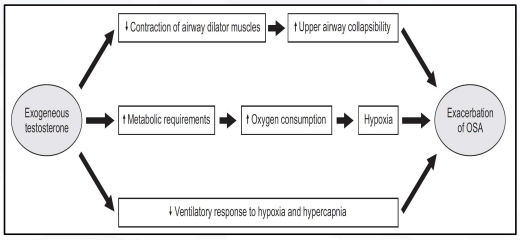
TD, Inflammation, and OSA



Kim SD, Cho KS. *World J Men's Health.* 2019; 37(1): 12-18.

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Putting it Together: a Symphony of Comorbidities

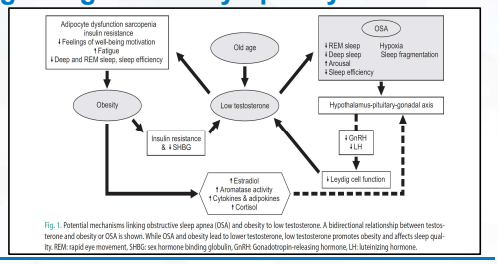

Fig. 1. Potential mechanisms linking obstructive sleep apnea (OSA) and obesity to low testosterone. A bidirectional relationship between testosterone and obesity or OSA is shown. While OSA and obesity lead to lower testosterone, low testosterone promotes obesity and affects sleep quality. REM: rapid eye movement, SHBG: sex hormone binding globulin, GnRH: Gonadotropin-releasing hormone, LH: luteinizing hormone.

References: Kim SD, Cho KS. *World J Men's Health.* 2019; 37(1): 12-18.

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TD Comorbidities Improved by TRT

- Inflammation
- Decreased Libido / Erectile Dysfunction
- Loss of Bone Mineral Density and/or Muscle Mass
- Metabolic Dysregulation: Obesity/IR/DM/Met-S
- Cardiovascular Disease (CVD)

TD Comorbidities with Unclear Relationship to TRT

- Cognitive Decline
- Prostate Health

TD Comorbidity NOT Improved by TRT

- Obstructive Sleep Apnea (OSA)

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TD: Expert's Agree

- TD is a global public health concern
- TD is a significant medical condition that negatively impacts male sexuality, reproduction, general health, and QOL
- Men with TD benefit from TRT regardless of whether an etiology is found
- The evidence does not support increased CV risk or prostate cancer risk
- TRT is effective in both young and older men
- TRT is effective and evidence based
- There is no T level that reliably distinguishes those who will respond vs those who will not respond to TRT

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Treating Low T

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Lifestyle Treatment

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Lifestyle Treatment

Consider before TRT

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Testosterone Deficiency Treatment

- Remember to consider Root Causes
- Start with Lifestyle
- Then Consider Testosterone Sparing Options
  - Must have functional gonads
- Testosterone Replacement Therapy (TRT)

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Lifestyle Options

- Stress Management
- Sleep
- Weight loss
- Intermittent Fasting
- Nutrition
- Movement- especially strength training

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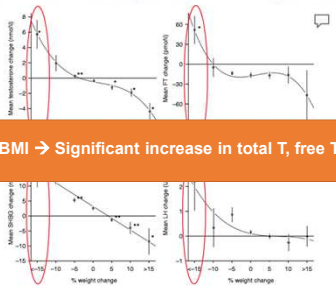
Mean Hormone Changes by % weight change



15% loss in BMI → Significant increase in total T, free T, and LH levels

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Weight Loss Affects on Serum T In Prediabetic Men

- 2012 Endocrine Society Presentation - Frances Hayes, MD
- **~900 men from the Diabetes Prevention Program US prediabetic study cohort**. Randomized:
- Patients given Lifestyle Intervention, Metformin or Placebo
- **Only Lifestyle group showed benefit** and found **46% decreased prevalence in hypogonadism at 1 year.**

References: Hypogonadism Reversal in Overweight Men with Prediabetes. EndocrineWeb. http://www.endocrineweb.com/professional/meetings/hypogonadism-reversal-overweight-men-prediabetes. Accessed May 30, 2018.

159

Free T Levels increase as Visceral Fat Quantity and Adipocyte Inflammation Resolve Bariatric Study vs Medical Weight Loss

Abstract

This study evaluated obese men with T2DM randomized to either bariatric surgery or medical therapy. Testosterone, gonadotropins, body composition, insulin sensitivity, and inflammatory markers were evaluated in 32 patients at baseline and at 5 years. Surgical patients had 47.4% increase in free testosterone compared to medical therapy patients who had 2.2% decrease ($P = 0.013$). Increase in free testosterone correlated with reduction in body weight, high-sensitivity C-reactive protein (hsCRP), and leptin levels. Prolonged improvements in testosterone levels after bariatric surgery in T2DM are found to be related to reduction in body weight and adipogenic inflammation.

References: Nathan H. Pham et al. Increased Free Testosterone Levels in Men with Uncontrolled Type 2 Diabetes Five Years After Randomization to Bariatric Surgery. Obesity Surgery January 2018, Volume 28, Issue 1, pp 277–280.

160

The Change in the Percent of Android and Gynoid Fat Mass Correlated with Increased Testosterone After Laparoscopic Sleeve Gastrectomy in Chinese Obese Men: a 6-Month Follow-Up

- **Objective**- The study was designed to examine changes of body fat distribution after laparoscopic sleeve gastrectomy (LSG) in obese male patients and to confirm whether these changes are correlated with increased testosterone.
- Fat mass was significantly decreased in all regions, but the loss of fat mass in the android region was more than that in any other body region.
- After adjusting age and the BMI, the changes in android FM% and gynoid FM% were significantly correlated with an increase in total testosterone concentration ($R^2 = 0.187$, $R^2 = 0.282$, respectively).

References: Jingyang Gao et al. Obesity Surgery, July 2018, Volume 28, Issue 7, pp 1960–1965

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The Change in the Percent of Android and Gynoid Fat Mass Correlated with Increased Testosterone After Laparoscopic Sleeve Gastrectomy in Chinese Obese Men: a 6-Month Follow-Up

Conclusion

- In obese male patients with BMI 30–45 kg/m^2, an increase of total testosterone correlated to the changes in android FM% and gynoid FM% at the sixth month after LSG surgery.

References: Jingyang Gao et al. Obesity Surgery, July 2018, Volume 28, Issue 7, pp 1960–1965

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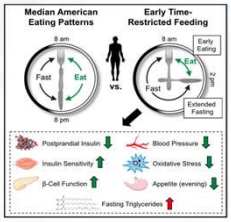
Secret Weapon to Reverse/Prevent -Obesity, DM2, Met-S, Leptin/Insulin Resistance to Optimize T

Intermittent Fasting **- eTRF**
(early Time Restricted Feeding) shown best.

- Has become my #1 tool for success with cardiometabolic diseases associated with TD!
- Best of all…NO SURGERY or complications of surgery!



References: Sutton et al., Early Time-Restricted Feeding Improves Insulin Sensitivity, Blood Pressure, and Oxidative Stress Even without Weight Loss in Men with Prediabetes . 2018, Cell Metabolism 27, 1212–1221 June 5, 2018 a 2018 Elsevier Inc. https://doi.org/10.1016/j.cmet.2018.04.010

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Why Intermittent Fasting?

- Free - no cuisine, powders, supplements, special foods. Saves $$
- Safe and Simple - The Un-Diet
- Powerful - same as Bariatric Surgery for reversing DM2, obesity all while maintaining lean body mass
- Flexible - anytime, anywhere, any protocol. Stop and start whenever. Fit it to your schedule
- Reverses most cardio-metabolic diseases
- Works even if cannot eat meat, nuts, dairy, gluten, lectins, etc.
- Works if you have no money or teeth or travel a lot

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Time Restricted Eating is Not the Same as Calorie Reduction Diets

- The inability of most diets to reduce insulin resistance is exactly why they eventually result in weight regain
- Fasting, on the other hand, introduces prolonged periods of low insulin levels, which breaks the cycle of high insulin and insulin resistance.
- It is the constant levels of insulin that prevent access to stored fat energy and lipolysis

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Time Restricted Eating is Not the Same as Calorie Reduction Diets

- If you maintain a constant calorie-reduced diet, the body quickly adapts to it and energy expenditure quickly declines to match reduce caloric intake…weight plateaus, then is regained. Not because you stopped your diet or have no self control, but because your body adapted to the new set point of energy availability.
- To prevent the body from adapting to the new weight-loss requires an *intermittent* strategy, not a constant one.
- RESTICTING SOME FOODS ALL THE TIME VS RESTRICTING ALL FOOD SOME OF THE TIME - This is the crucial difference

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The "Eat Less, Move More" Strategy for Daily Caloric Reduction Doesn't Provide These Hormonal Benefits Needed

- The sudden, severe caloric reduction seen after bariatric surgery allows the same hormonal adaptations seen during fasting that keeps resting metabolic rate steady, unlike what happens with gradual, continued caloric reduction.
- Head to head studies reveal that fasting is actually superior to bariatric surgery in both weight loss and reduction of blood sugars.
- Both fasting and bariatric surgery are effective for DM2 reversal

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References on Fasting and Bariatrics

- Furmli S, *et al*. Therapeutic use of intermittent fasting for people with type 2 diabetes as an alternative to insulin. *BMJ Case Rep* 2018. doi:10.1136/bcr-2017-221854
- Mathew P Matson, Valter D Longo, Michelle Harvie. Impact of intermittent fasting on health and disease processes. Ageing Research Reviews, Volume 39, October 2017, Pages 46-58
- *Sai Krupa Das et al.*Long-term changes in energy expenditure and body composition after massive weight loss induced by gastric bypass surgery1 Am J of Clin Nutr 2003; 78: 23-30
- Erin Fothergill et al. Persistent Metabolic Adaptation 6 Years After "The Biggest Loser" Competition. Obesity; 24: 8: 1612-1619. 1 Aug 2018
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- Samuel Klein et al. "Absence of an Effect of Liposuction on Insulin Action and Risk Factors for Coronary Heart Disease," NEJM 350, 25(2004): 2549-57
- Ildiko Lingvay et al. Rapid Improvement in Diabetes After Gastric Bypass Surgery: Is it the Diet or Surgery? Diabetes Care, 36;9(2013):2741-7

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Who Needs TRT?

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Endocrine Society Guidelines for Testosterone Replacement – 3/17/18

1. Only in men with signs & symptoms consistent with low T.
2. Consistent low fasting, AM total testosterone, with confirmation on 2nd day.
3. Check SHBG if low normal Total T levels found.
4. Check free T (equilibrium dialysis method) if conditions exist that alter SHBG: old age, cirrhosis, hepatitis, DM2, high BMI, HIV, anticonvulsants, HRT, thyroid dz, nephrotic syndrome, use of glucocorticoids, acromegaly.

References: Shalender Bhasin et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guidelines. 2018 March 17. The Journal of Clin. Endo & Metab, jc. 2018-002299, https://doi.org/10.1210/jc.2018-002299

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Endocrine Society Guidelines 3/17/18

5. Additional labs to ascertain cause of TD: primary or secondary type – FSH and LH.
6. Discuss risk and benefits with patient decision making.
7. Induce and maintain secondary sex characteristics and correct symptoms of low T.

References: Shalender Bhasin et al. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guidelines. 2018 March 17. The Journal of Clin. Endo & Metab, jc. 2018-002299, https://doi.org/10.1210/jc.2018-002299

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Endocrine Society Guidelines 3/17/18

8. Recommend against if:
   - Planning fertility in near future
   - Breast or prostate cancer, *prostate nodule/induration, PSA>4 or >3 (if African American or 1st degree family member dx with Pca)
   - Elevated HCT>48 or >50% if lives at high altitude
   - Untreated obstructive sleep apnea
   - Severe lower urinary tract symptoms (IPSS>20)

**without further urologic work up*

References: Shalender Bhasin et al. Testosterone Therapy in Men With Hypogonadism: An Endrocrine Society Clinical Practice Guidelines. 2018 March 17. The Journal of Clin. Endo & Metab, jc. 2018-002299, https://doi.org/10.1210/jc.2018-002299

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Endocrine Society Guidelines 3/17/18

- Uncontrolled Heart Failure
- Myocardial infarction or stroke in last 6 months
- Thrombophilia (Factor V Leiden, Anti Cardiolipin Ab, history of venous thrombo-emb)

9. Men > 65 y/o meeting diagnostic criteria discuss risk vs benefits

Monitoring

Assess therapeutic effect, serum T levels, HCT, PSA few times during first year then annually if stable.

References: Shalender Bhasin et al. Testosterone Therapy in Men With Hypogonadism: An Endrocrine Society Clinical Practice Guidelines. 2018 March 17. The Journal of Clin. Endo & Metab, jc. 2018-002299, https://doi.org/10.1210/jc.2018-002299

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Conditions in Which T Administration Is Associated With a High Risk of Adverse Outcomes and for Which We Recommend Against Using T – 2018 Endocrine Society

Very high risk of serious adverse outcomes
Metastatic prostate cancer
Breast cancer
Moderate to high risk of adverse outcomes
Unevaluated prostate nodule or induration
Unevaluated PSA >4 ng/mL (>3 ng/mL in individuals at high risk for prostate cancer, such as African Americans or men with first-degree relatives who have prostate cancer)
Hematocrit > 48% (>50% for men living at high altitude)
Severe LUTS associate with benign prostatic hypertrophy as indicated by AUA/IPSS > 19
Uncontrolled or poorly controlled congestive heart failure
Desire for fertility in the near term

Adapted with permission from Bhasin et al. (7).Abbreviations: AUA, America Urological Association; IPSS, International Prostate Symptom Score.

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Assessment and Questionnaire for Low T in Aging Men (>50)

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Who is a Good Candidate for T Support?

- **Medical History**
  - **Individualized approach with questionnaires**

  -Signs & Symptoms using:

  -ADAM/SHIM/IPSS

Others:

- AMS-Aging Male Symptoms Scale
- MMAS-Massachusetts Male Aging Score

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Male Questionnaires- ADAM & SHIM

Table 1.
Questions Used as Part of the Saint Louis University ADAM Questionnaire

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

Note: A positive questionnaire results is defined as a "yes" answer to questions 1 or 7 or any 3 questions.

SEXUAL HEALTH INVENTORY FOR MEN (SHIM)

PATIENT NAME: _____ TODAY'S DATE: _____

PATIENT INSTRUCTIONS

Sexual health is an important part of an individual's overall physical and emotional well-being. Erectile dysfunction, also known as impotence, is one type of very common medical condition affecting sexual health. Fortunately, there are many different treatment options for erectile dysfunction. This questionnaire is designed to help you and your doctor identify if you may be experiencing erectile dysfunction. If you are, you may choose to discuss treatment options with your doctor.

Each question has several possible responses. Circle the number of the response that **best describes** your own situation. Please be sure that you select one and only one response for **each question**.

OVER THE PAST 6 MONTHS:

		Very Low	Low	Moderate	High	Very High
1. How do you rate your confidence that you can get and keep an erection?		1	2	3	4	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	No Sexual Activity	Almost Never or Never	A Few Times (Much Less Than Half the Time)	Sometimes (About Half the Time)	Most Times (Much More Than Half the Time)	Almost Always or Always
	0	1	2	3	4	5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Did Not Attempt Intercourse	Almost Never or Never	A Few Times (Much Less Than Half the Time)	Sometimes (About Half the Time)	Most Times (Much More Than Half the Time)	Almost Always or Always
	0	1	2	3	4	5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did Not Attempt Intercourse	Extremely Difficult	Very Difficult	Difficult	Slightly Difficult	Not Difficult
	0	1	2	3	4	5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Did Not Attempt Intercourse	Almost Never or Never	A Few Times (Much Less Than Half the Time)	Sometimes (About Half the Time)	Most Times (Much More Than Half the Time)	Almost Always or Always
	0	1	2	3	4	5

Add the numbers corresponding to questions 1-5. TOTAL: _____

The Sexual Health Inventory for Men further classifies ED severity with the following breakpoints:

1-7 Severe ED 8-11 Moderate ED 12-16 Mild to Moderate ED 17-21 Mild ED

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International Prostate Symptoms Score - IPSS


MIMS CLINICAL SPECIAL

INTERNATIONAL PROSTATE SYMPTOM SCORE (I-PSS)

Patient Name: _____ Date of birth: _____ Date completed _____

In the past month:	Not at All	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always	Your score
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it difficult to postpone urination?	0	1	2	3	4	5	
5. Weak Stream How often have you had a weak urinary stream?	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	1 Time	2 Times	3 Times	4 Times	5 Times	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

The first seven questions of the I-PSS are identical to the questions appearing on the AUA Symptom Index which categorizes symptoms according to the symptom score range as follows:

Mild (1-7) – Moderate (8-19) – Severe (20-35)

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

The SCI strongly recommends that all physicians who counsel patients suffering from lower urinary tract symptoms utilize these measures not only during the initial interview but also during and after treatment in order to monitor response. Prop. May 2013

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How to Give TRT?

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Modes of Delivery for TRT

- Transdermal Cream
- Transdermal Gel
- Injection
- Pellet
- Patches
- Sublingual/Buccal/Troche
- Oral BLA (Bio-Lymphatic Absorption)
- Nasal

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Modes of Delivery for TRT

- Transdermal Cream
- Transdermal Gel
- *Injection*
- Pellet
- ~~Patches~~
- ~~Sublingual/Buccal/Troche~~
- ~~Oral BLA (Bio-Lymphatic Absorption)~~
- ~~Nasal~~

Uncommon Deliveries

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Modes of Delivery for TRT

- Transdermal Cream
- Transdermal Gel
- Injection
- Pellet

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Testosterone Pellets

Very high doses are common in the pellet industry. Consider using only if you are willing to become an expert. Suggested dose is 800-1200mg, but many use as much as 2400mg.

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Testosterone Pellets

- Pros
  - Easy for patients – no daily, weekly, bi-weekly dosing
  - Delivers stable, steady testosterone dosing for ~ 4 months
    - Dose dependent on baseline testosterone level
    - When dosed correctly, minimal, if any, erythrocytosis
  - Testing via serum: 800ng/dL - 1200ng/dL
    - Urine (DUTCH) for metabolites: T and E
- Cons
  - Requires an insertion
  - Risk of extrusion if patient not counseled correctly
  - Infection risk if insertion not done carefully and skillfully
  - Cannot easily adjust dose if give too much

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Common Modes of Delivery for TRT

- TD Cream – Compounded only
- TD Gel – FDA approved or compounded
- Injection – FDA approved or compounded

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Testosterone Creams and Gels

- Gels (Androgel™) are the most popular TRT
- May have variable absorption
- Risk of secondary exposures (wives, kids, pets)
- Generally, start at 50mg - can titrate up to 150mg
- Target normal serum levels

- Data suggests creams do not absorb as well as gels
  - May need higher doses (2X) for similar serum T

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Testosterone Injections

- More erythrocytosis than gels
- Less convenient, pain at injection site
- Fluctuating mood/libido

- I Prefer Testosterone Cypionate (8-day ½ life)
  - Injections also available as:
    - Enanthate (10-day ½ life)
    - Propionate (5-day ½ life)
    - Undecanoate (long lasting)

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Testosterone Cypionate Injections

- Testosterone Cypionate (8-day ½ life)
  - I prefer bi-weekly IM 40-60mg
  - Weekly IM 100mg common
  - Can use every 2 weeks, 200mg (poor option)
- More E2, less DHT compared to gels

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Things to Watch for With TRT

- Acne
- Apnea
- Decrease in HDL to LDL (good to bad cholesterol) ratio (controversial)
- Depression (can help as well)
- Edema due to fluid and electrolytes retention
- Increased or decreased libido
- Non-infectious Hepatitis
- Psychological issues
- Polycythemia – stop if HCT 54 or higher DVT/PE-data shows more a permissive association
- Insomnia
- Liver cell tumors – 1st gen oral meds
- Male pattern baldness
- Nausea/Vomiting

- Bladder irritability
- Gynecomastia
- Increased frequency of erection
- Inhibition of testicular function infertility (azo or oligospermia)
- Testicular atrophy

- **Urology Consult Required When:**
- Abnormal DRE
- PSA > 4 at anytime
- PSA increase > 1.4 over a 12 month period after initiating therapy
- Worsening LUTS

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How to Test TRT?

Ask the other Mark!
(coming up later)

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A Classic Example of TRT

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Patient Profile

- Aging male with low T symptoms and no obvious contributions from root causes
- Serum T<300ng/dL, moderately elevated LH
  - Normal E2, SHBG, FSH
  - No DUTCH Test (budget conscious, saving for follow-up)
- Treatment directly related to T (beyond lifestyle)
  - Elevated LH implies potentially poor gonadal function
  - Testosterone-Cyp injections twice/week, 50mg
- Follow up labs (serum, DUTCH) at 6 weeks
  - Injections on Monday/Thursday, testing on Wednesday

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Patient Profile – Follow Up

- Improved symptoms profile
- Serum T=550ng/dL (likely higher 2 days before test)
- Normal LH
- DUTCH – what I hope to see
  - Normal (not high) estrogen (E2 and other metabolites)
  - Optimal phase 1 estrogen metabolism (not 4-OH preferred)
  - At least decent estrogen methylation
  - High normal T
  - Epitestosterone likely <10 (implies gonadal suppression)
  - Also check on OATs (especially pyroglut.), melatonin, 8-OHdG, DHEA and cortisol

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What if He's making too much E2?

- May present with gynecomastia
- Address things up-regulating aromatase
  - Inflammation
  - Insulin
  - Leptin
  - Age
  - Stress (cortisol)

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What if He's making too much E2?

- May consider Anastrozole (0.5mg 2x/week)
  - Want E2 25-35pg/mL
  - Monitor estrogen metabolism
- Chrysin ??

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Patient Profile – Follow Up

- Remember to take care of the whole patient. If you fix low T and ignore gut, thyroid and adrenal (HPA axis) issues, sustainably improved health will be elusive.

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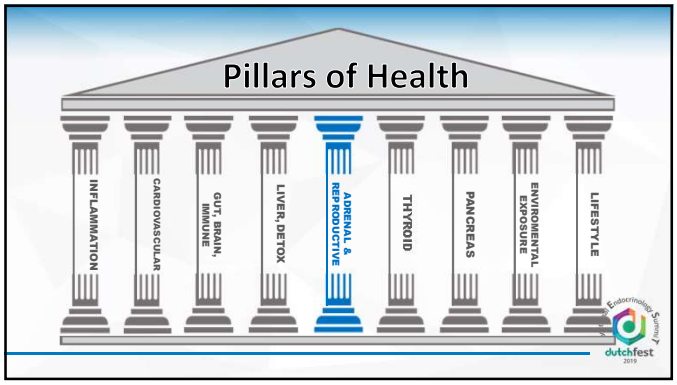

197

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