

TESTOSTERONE REPLACEMENT THERAPY

-A RECIPE FOR SUCCESS-

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“Everything You Always
Wanted to Know About TRT
But Didn’t Have Time to Ask”

WHAT IS TESTOSTERONE REPLACEMENT THERAPY (TRT)?

TRT: Restoration of
Testosterone to HEALTHY
physiological levels.

TRT is NOT:

- Total T > normal range
- Steroids
- Viagra

SCREENING FOR
HYPOGONADISM

WHAT ARE THE SYMPTOMS OF LOW TESTOSTERONE?

- TAT Syndrome
- Fatigue
- USTA Syndrome
- Loss of muscle mass
- Fat gain
- Poor recovery
- Pain/Inflammation
- Irritability
- Depression
- Decreased memory
- Loss of Libido
- Erectile Dysfunction

ADAM Questionnaire

1. Do you have a decrease in 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?

ADAM Questionnaire (con't)

6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Has it been more difficult to maintain your erection throughout sexual intercourse?
9. Are you falling asleep after dinner?
10. Has your work performance deteriorated recently?

INITIAL LAB WORK

INITIAL HYPOGONADISM PANEL

- Total Testosterone
- Bioavailable/Free T
- SHBG
- DHT (?)
- LH/FSH
- DHEA-S
- Estradiol
- Estrone
- Prolactin
- Progesterone
- Cortisol
- Thyroid Panel (TSH, FT4, FT3, reverseT3)
- Chemistries
- CBC
- Lipid Panel
- PSA (if over 40)

MEASURES OF TESTOSTERONE

- **Total Testosterone**—all that is produced
...most commonly used to deny TRT
- **Free Testosterone**—all that is unbound (1-4%)
...can be misleading compared to Bio T
- **Bioavailable Testosterone**—Gold Standard
“Free and Loosely/Weakly Bound” (40-60%)

“Laboratory reference values for testosterone vary widely, and are established without clinical considerations.”

Lazarou S, et al. Harvard Medical School, Division of Urology, Beth Israel Deaconess Medical Center

Higher Death Risk in Men With Lower Testosterone Levels

Circulation, Dec. 4, 2007; vol 116, Kay-Tee Khaw, MBBCh, professor of clinical gerontology, University of Cambridge, England. Robert Davis, MD, professor of urology, University of Rochester, N.Y.

Compared to lowest quartile
WITHIN NORMAL RANGE:

- **Men in the second lowest quartile (Q2) were 25% less likely to die.**
- **Men in the second highest quartile (Q3) were 38% less likely to die.**
- **Men in the highest quartile (Q4) were 41% less likely to die.**

COMMON SENSE

A Total Testosterone of 500 (ng/dL) in a range of 250-1000 (ng/dL) is NOT “midrange”.

It is instead 1/3 of the way up from the bottom.

COMMON SENSE

The top of “normal range” for one laboratory is equal to the top of “normal range” at another.

T SAMPLE PREPARATION (SERUM)

- Refrigerated, no additive serum preferred (Plain, Red Top tube)
- Heparanized serum less acceptable (green-top)
- NO Serum Separator Tubes (SST)

ABOUT ESTROGEN TESTING

- Total Estrogens is NOT a valid assay for adult males on **serums**
 - assay "tuned" for adult female range
 - standard Estrogen assays overestimate
 - so may lead to inappropriate AI use
- Estradiol MUST be "sensitive" method
- Be extra mindful of SHBG level

ACCEPTABLE ESTRADIOL TESTS--SERUM

- Quest Diagnostics "Ultrasensitive Estradiol"
 - Code #30289
- LabCorp "Sensitive Estradiol"
 - Code # 140244 (RIA) (less \$)
 - Code #500108 (LC/MS) (more \$)
- Mayo Clinic "Enhanced Estradiol"
 - Code # 81816

ACCEPTABLE ESTROGEN TESTS--URINE

- 24 hour urines (LC/MS/MS) valid for males for all Estrogens
- 2-OHE, 4-OHE, 16-OHE of value
- E metabolites, pathways, Phase I and Phase II detox (not valid if $E1 < 5$ on urines)
- Need Total T, SHBG to evaluate

SHBG

- Sex Hormone Binding Globulin
- Produced by liver (et al)
- Binds sex hormones-- androgens and estrogen, androgens > estrogen
- ↑ by E, liver failure, growth hormone, hyperthyroidism, Thyroid Tx
- ↓ by androgen, IGF-1, insulin
- No real way to manipulate

SHBG (cont)

- Low SHBG frees up T, but also E
- Low SHBG → URINARY HYPEREXCRETION
- Low SHBG assoc with **Anxiety**
- Lower SHBG better for un-treated
- High SHBG better than low for those on TRT

SHBG *key points*

- The centerpiece of hormonal evaluation
- Largely determines bioavailable levels
- Rescue cases otherwise missed
- Directs subsequent TRT modality
- Predictor of anxiety

SAMPLE MATRIXES

Blood

- most common
- quick reporting
- common for insurance company reimbursement
- Total, Free, Bioavailable
- "snap shot" only
- limited value b/c pulsatile hormonal production, TD's, hormone conversions

SAMPLE MATRIXES

Urine

- best of all, esp. w/ TD's, get the AUC!
- "Free" levels provided
- get **serum** TT and SHBG at same time
- expanded hormones, metabolites
- use only 24 hour collections—no spots
- be careful of contamination
- better to assess pathways, 5-AR activity
- No oral DHEA! TD DHEA okay

Many times T on bloods (especially for morning draw) will be well within normal range. But when you collect a 24 hour urine, T will be deficient. Thus a spurt of T in the morning, then very little the rest of the day.

COMMON SENSE

IN ORDER TO TEST THE LEVEL OF A DRUG, YOU MUST TAKE THE DRUG, ON SCHEDULE!

COMMON SENSE

HAVE PATIENT APPLY AND DRAW AT SAME TIME OF DAY EACH TIME WITH TRANSDERMALS (b/c PK's)

DHT

- Most responsible for All Things Male
- 5-AR'd from T
- Unfairly deemed "evil hormone"
- NOT responsible for prostate morbidity
- 25-75ng/dL
- Serum assay valid?
- Metabolite ratios on 24 hour urines best
- Avoid finasteride

Estradiol/Estrone

- MUST be monitored during TRT
- Masks benefits of TRT
- Adjunctive cause of serious illness
- Numerous benefits for health, so...
- Must not be driven too low
- Maintain mid-range (w/ mid-range SHBG)
- May rise over time
- TD's elevate E more than IM

Luteinizing Hormone (LH)

- Produced by pituitary
- Stimulates T production, et al
- Pulsatile production
- Short half-life
- Acute phase reactant
- Must be careful in its interpretation
- Possible Gn-secreting tumor

Follicle Stimulating Hormone (FSH)

- Produced by pituitary
- Spermatogenesis
- 180-240 minute half-life
- Inhibited largely by estrogen
- Better measure of gonadotrophin output?
- Possible FSH-secreting tumor

PROLACTIN

- Significant cause of hypogonadism
- May signal tumor presence
- Health benefits
- Must be maintained within normal range
- Ref Range (3.0-18.0 ng/mL)
- >300= tumor
- Elevated by eating, sex (<30)

HYPERPROLACTINEMIA CAUSES

- | | |
|--------------------------|---------------------|
| ▪ Pituitary tumor | ▪ Opiates |
| ▪ Stalk compression | ▪ Tri-cyclics |
| ▪ Primary hypothyroidism | ▪ D2 antagonists |
| ▪ Chronic renal failure | ▪ Metoclopramide |
| ▪ Cirrhosis | ▪ Verapamil |
| | ▪ Chest wall trauma |

Cortisol

- "Stress hormone"
- Cause of secondary hypogonadism
- Healthful benefits
- Must be maintained within normal range
- If elevated: Tx'd Phosphatidylserine (PS) (start at 300mg po qhs)
- If depressed: Adrenal Fatigue Tx's

PROGESTERONE for ADULT MALES

- FEMINIZING EFFECTS
 - elevates SHBG
 - powerfully inhibits HPTA
 - can cause gynecomastia
 - cause impotence/lack of libido
- Give PREG transdermal instead
 - flow down pathways, prevents above

T/E ratio

- Measure of system performance
 - ratio does have importance, but...
 - absolute values of hormones are much more important
 - cannot elevate E without consequence, even when T is proportionately high
- Used to explain pathophysiology:
 - Low T → higher proportionate E → morbidity
- NOT a treatment goal

LABS (con't)

- Thyroid Panel (TSH, FT4, FT3, rT3)
- CBC (anemia mimics ↓T)
- Comprehensive Metabolic Panel
- Lipid Profile
- PSA (if over 40)



TESTOSTERONE DELIVERY SYSTEMS

- Gels and Creams
- Patches
- Implantable Pellets
- IM
- Orals

Gels and Creams

- Ease of application
- May be more convenient—OR NOT
- Stable across week, not day
- "Pulsing" [T] very beneficial
- 2 pumps BID >>> 4 pumps QD
- Quickly attains stable levels
- Boosts DHT
- May elevate estrogens > shots

Gels and Creams

- ONLY USE GELS, NOT CREAMS
- Risk of accidental transfer
- Be mindful of application method
- Avoid antecubital fossa—looks like AAS
- EXTREMELY variable absorption
- ...IF poor, consider thyroid, emolient

Gels and Creams (con't)

- “Big House” products:
Androgel, Testim, Fortesta, Axiron
 - MUCH more expensive
 - support physician education (“The Cause”)
 - covered by insurance
 - vouchers/samples
 - 1-2% concentration
 - be mindful of application technique

Gels and Creams (con't)

- Compounded gels/creams
 - various bases—GELS NOT CREAMS!
 - 1%, 5%, 10, 20%
 - higher conc. → < E, DHT conversion
 - soy, yam-based T's
 - ALL T gels/creams are “bio-identical”
 - creams slow absorption, and cause waste
 - Chrysin is dead
 - MUCH less expensive

T GEL APPLICATION

- Jars with measuring spoons
- Plastic capped syringes
- Metered Dose Pumps (my favorite)
- Use same base, sites for all TD's
- 1% apply to outer arms, shoulders, flanks
- 5%, 10%, 20% applied to forearms
- Don't use palms to rub in!

Testosterone Patches

- Convenient—MAYBE!
- No risk of accidental transfer
- Stable serum androgen levels
- Little DHT, E boost
- Scrotal patches available
- 2/3 >Contact Dermatitis

IMPLANTABLE PELLETS

- Provide long half-life
- Some patients consider them convenient
- Billable office procedure
- Extrusion risk is technique dependent
- Increased risk of scarring, pain
- No one knows the PK's of T pellets
- Are NOT physiologic

Testosterone Injection

- Convenient—MAYBE!
- MUST be injected weekly
- Stable across day, not week
- Ease of dose titration
- Injection risks
- The “Gold Standard” no more

NEEDLE SIZES

- Glutes: 22ga 1 ½”
- Thighs: 25ga 1”
- SubQ: 25ga 5/8”>29ga

WHAT ABOUT TESTICULAR ATROPHY?

OTHER MEDS: hCG

- Human Chorionic Gonadotropin
- Luteinizing Hormone (LH) analog
- Not just a “fertility drug”
- Traditional treatment for secondary hypogonadism, testicular atrophy
- May not provide subjective benefits of TRT
- Best use is adjunctive for TRT
- “Backfill” normal hormonal pathways
- Subcutaneous injection

OTHER MEDS: SERM's

- Selective Estrogen Receptor Modulator
- Elevates Gonadotropins→ ↑Testosterone
- May not bring subjective benefits of TRT
- Half of SERM is estrogen agonist, so may bring high estrogen symptoms
- Low dose Tx
- Useful for testing Hypothalamic-Pituitary-Testicular Axis (HPTA)
- Useful for restarting HPTA
- Useful for treating gynecomastia

SERM's (con't)

- Clomiphene
 - enclomiphene + zuclomiphene
 - may bring untoward visual effects
 - may bring untoward emotional effects
 - 12.5mg PO QD starting dose>50mg QD
- Tamoxifen
 - developed for Breast CA Tx
 - great for “nipple issues”
 - ↑ progesterone receptor density
 - 5mg PO QD starting dose>20mg qd

CONTRAINDICATIONS TO TRT:

- Prostate CA (for now!)
- Breast CA
- Untreated prolactinoma

RELATIVE CONTRAINDICATIONS:

- Prostate-Specific Antigen (PSA) >4.0 or acceleration >0.75/year
- H/H > 18/55
- Sleep Apnea
- Cardiac, Hepatic, Renal Dz

POTENTIAL RISKS (listed)

- Increased risk of bladder outlet symptoms due to increase in prostate volume—NO!
- Edema in patients with preexisting cardiac, renal, or hepatic disease
- Gynecomastia
- Polycythemia (monitor H/H)
- Precipitation or worsening of sleep apnea
- Acne
- Decreased sperm production
- Stimulation of growth in previously undiagnosed prostate cancer—NO!

DRUG INTERACTIONS:

- Diabetic Medications
- Propranolol
- Oxyphenbutazone

The Meat and Potatoes of TRT

INITIAL DOSAGES

- **Transdermal gels ("TD's")**
50mgs total QD
5mgs (delivered to bloodstream)
--give careful application instructions
- **Testosterone Injectable:**
80mg IM QW
--initial double dose "front load"?
--split weekly dose for those with low SHBG or estrogen issues

FOLLOW-UP LABS

- Total T
- Bio T
- LH/FSH (especially with TD)
- FSH—to back up LH interpretation of HPTA status
- SHBG
- Estradiol /Estrone
- CBC
- Comp. Metabolic Panel
- PSA (if over 40)

SUBCUTANEOUS TESTOSTERONE INJECTIONS!

Subcutaneous administration of testosterone. A pilot study report.

[Al-Futaisi AM, et al. 2006](#)

“Therapy with weekly subcutaneous testosterone produced serum levels that were within the normal range in 100% of patients for both peak and trough levels.”

STABLE TESTOSTERONE LEVELS ACHIEVED WITH SUBCUTANEOUS TESTOSTERONE INJECTIONS

M.B. Greenspan, C.M. Chang

“A once-week SC injection of 50–100 mg of TE appears to achieve sustainable and stable levels of physiological T. This technique offers fewer physician visits and the use of smaller quantity of medication, thus lower costs.”

Evaluation of the efficacy of subcutaneous administration of testosterone in female to male transexuals and hypogonadal males

Jerrold Steven Olshan, MD, et al

“SC T was well tolerated and produced therapeutic serum concentrations at doses generally lower than required for IM injections.”

SUBCUTANEOUS TRT

- No more holes in muscles
- Reduces increase in estrogen
- BIW dosing makes serum saw pattern
- Better for those with lower SHBG
- Increases in libido over weekly IM
- (Tues, Fri) schedule is best
- Needle size highly patient specific
- Use a one piece rig

FOLLOW UP LABS (con't)

- Initial F/U at 2 weeks with TD
 - stable serum T levels quickly attained
 - logistical consideration of 30-day dose
- Initial F/U at 4 weeks with Injectable
 - takes that long to equilibrate
 - interpret by PK's of T ester (48-72 hour peak)
 - no greater than 7 day shot interval
- F/U at 4 weeks S/P dosage change or estrogen control s/p HPTA-suppression

FOLLOW-UP LABS (con't)

- Once dose is titrated:
 - q 6 months or yearly
 - Include PSA
 - Perform Digital Rectal Exam (DRE)

TIMING OF LABS FOR SHOTS

- Cypionate, Enanthate esters peak at 48-72 hours s/p IM injection
- Decline thereafter
- $T_{1/2}$ = 5-8 days
- No lab draw on injection day!
 - no urines first three days
- Same day of injection week each time
- Draw serums last half of injection week
- Use these facts to interpret labs

TIMING OF LABS FOR TD's

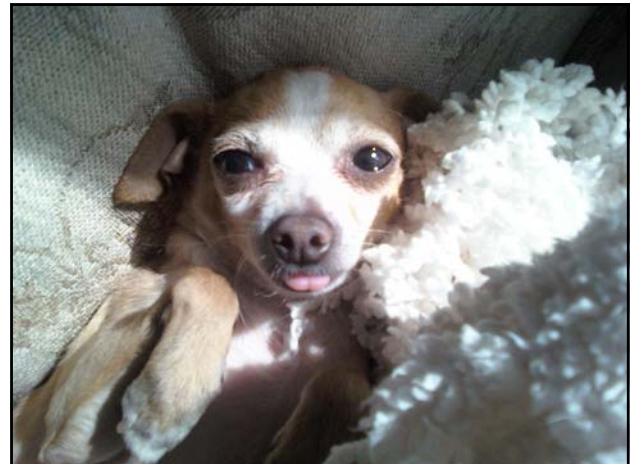
- Apply at same time each day
- Always ask pt. when they apply (lifestyle)
- Split dose?
- Consider TD carrier!
- Allow at least 2 hours prior to draw
- 2-4 hours is best with T gels
- Above no problem with 24 hour urines
- Absorption is slowed, lost with T creams

ESTROGEN ISSUES

- Do not Tx until post F/U labs
 - E2 may actually DROP with TRT
 - insight into body's response
- Maintain E2 at mid-range, or lower (with mid-range SHBG)

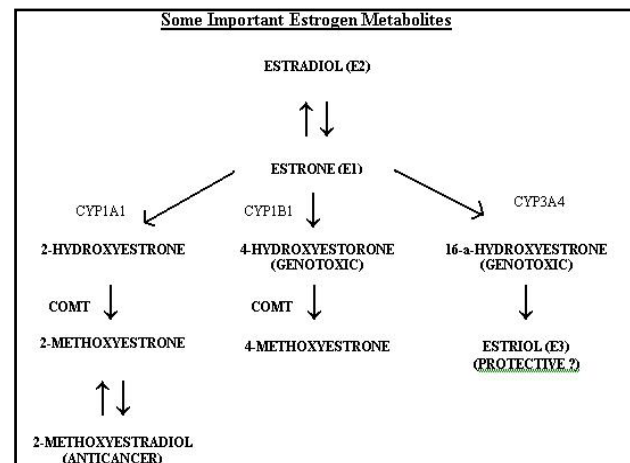
Detriments of ELEVATED Estrogen

- | | |
|-----------------------------|------------------------------|
| ▪ Suppresses HPTA | ▪ Increases clotting factors |
| ▪ Elevates SHBG | ▪ Water retention |
| ▪ Impotence | ▪ Prostate morbidity |
| ▪ Infertility | ▪ Cancers |
| ▪ Psychological morbidities | ▪ Female fat distribution |
| ▪ Vasospasm | ▪ Fx on thyroid function |
| ▪ Hypertension | ▪ ↑ "Wimpy Factor" |



Detriments of DECREASED Estrogen

- Damage to Lipid Profile
- Bone demineralization
- Decreased sex drive
- c/o headaches, multiple arthralgias



ESTROGEN ELEVATORS

- Age
- Obesity
- ETOH over-consumption (incl HOPS in beer!)
- Liver Dz
- Zinc deficiency (50mg Zn/2mg Cu QD)
- Vitamin C deficiency
- Excessive DHEA supplementation (100mg QD)
- Androstenedione supplementation
- Xenoestrogens (incl Vinyl IV bags!)
--Lavender, Tea Tree Oil
- Liver Detoxification issues
- Soy
- Flax seed
- Foods

ANASTRAZOLE

- Aromatase ("Estrogen synthase") Inhibitor
- "Competitive" Inhibitor > "Suicide" Inhibitor
- #1 use of this med in world: Male TRT
- other AI's available
- concerns with Endocrine pathway disruption (as with finasteride)
- c/o H/A's, arthralgias = E too low
- AI's as sole TRT is RARE (use very small dose)

ANASTRAZOLE DOSING

- 0.25mg QOD, 0.5mg Q2-3D (starting dose)
- On shot day(s) to inhibit peak
- 2 day t $\frac{1}{2}$
- Titrate from there
- Allow 4 weeks prior to f/u labs
- Remember SHBG may ↓

SHBG ISSUES (lower)

- More Free/Bioavailable T, but also E!
- ↑ urinary excretion of T, but not E!
- Risk of ANXIETY↑↑
- Shots much better than TD's
- Use smaller doses with more frequent dosing schedule for injections
--SC injecting is great for this!
--BIW>QOD dosing

SHBG ISSUES (higher)

- Lowers Free/Bio T, less Free/Bio E too
- Need a larger pulse of T to overcome
--stick with weekly dosing
--less chance of using SC injections
- GIVEN THE CHOICE, I WOULD TAKE HIGHER SHBG OVER LOWER (while on TRT)

CRISLER HCG PROTOCOL

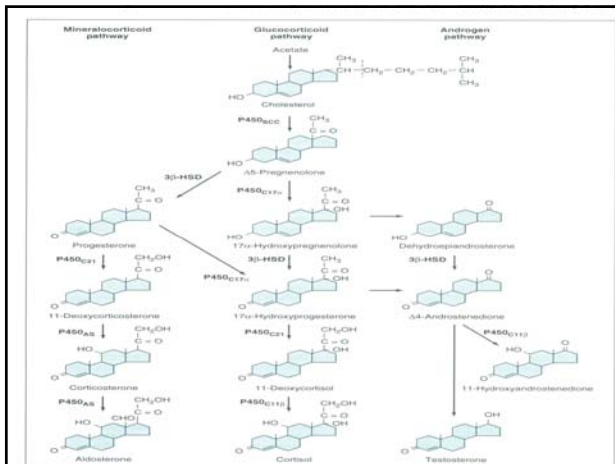
- 250IU twice per week with weekly shots
- Low Dose QD (100iu QD) with TD's
- ABOVE ARE STARTING DOSAGES
- NEVER more than 500IU at a time
--greatly elevates estrogen, progesterone
- SC injections only—NO IM!
- Weekly Testosterone injection patients:
T-2/T-1 days prior to injection

CRISLER HCG PROTOCOL (con't)

- For weekly shot patients:
 - evens out serum androgen levels by t1/2 of cypionate ester
- Prevents testicular atrophy
- Fertility protection
- Stimulates all three CHOL pathways
- Abundant boost in libido/sense of well being

RESTORING PATHWAYS ("backfilling")

- HCG
 - TRT induces secondary hypogonadism
 - this lowers CHOL>PREG
 - LH analog incr P450scc enzyme activity
- DHEA
 - TD is best 50-100mg QD in gel
 - 25mg BID oral
 - 100mg PO QD can elevate E1
 - TD>PO SR>standard oral preparation
- Pregnenolone
 - 50-150mg TD QD



Rescue from "Nipple Issues"

- Burning, itching, swelling, FREAKING
- Occurs with mere changes in hormones
- DO NOT treat in first month
- 20mg BID tamoxifen until gone, then taper
 - cut dose Q5D
- Prefer tamoxifen over clomiphene
- Cannot really assay estrogens on SERM-class drugs
- Hold GHRT (magnifies E fx)
- Gyno may be caused by progesterones

NO TRT "CYCLING"

- Historically "borrowed" from AAS use.
- No evidence of benefit
- Does not do what is claimed
- Leaves substantial periods of letdown
- The body thrives on regularity
- Learn your job!!!

WHAT IS THE FUTURE OF TRT?

- Elevating T to healthy, happy levels
- Estrogen metabolism
- Actions at the androgen, estrogen receptors
- Restoring endocrine pathways
- Bringing "conventional medicine" to our "evidence-based medicine"

THE GOAL?

“The ultimate goal of TRT medicine is to optimize health and happiness in our patients, which means producing an environment where we have elevated testosterone to sufficient levels, with the body responding as if unaware of the exogenous manipulations.”

--John Crisler, DO