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Panel Discussion: Challenging Cases in Hypogonadism

Case #1

Testosterone Supplementation and Prostate Cancer

Case #1

History:

- 56 yo male
- Referred for ED and low libido for 5 years
- ED poorly responsive to PDE5i's
- Normal DRE

Labs:

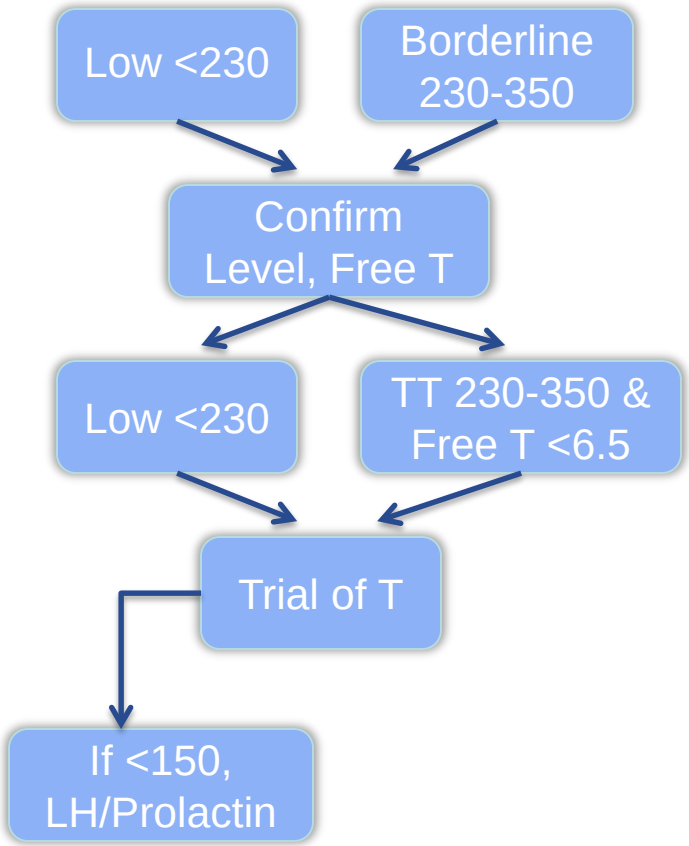
- PSA 1.9
- Total T 210

Case #1

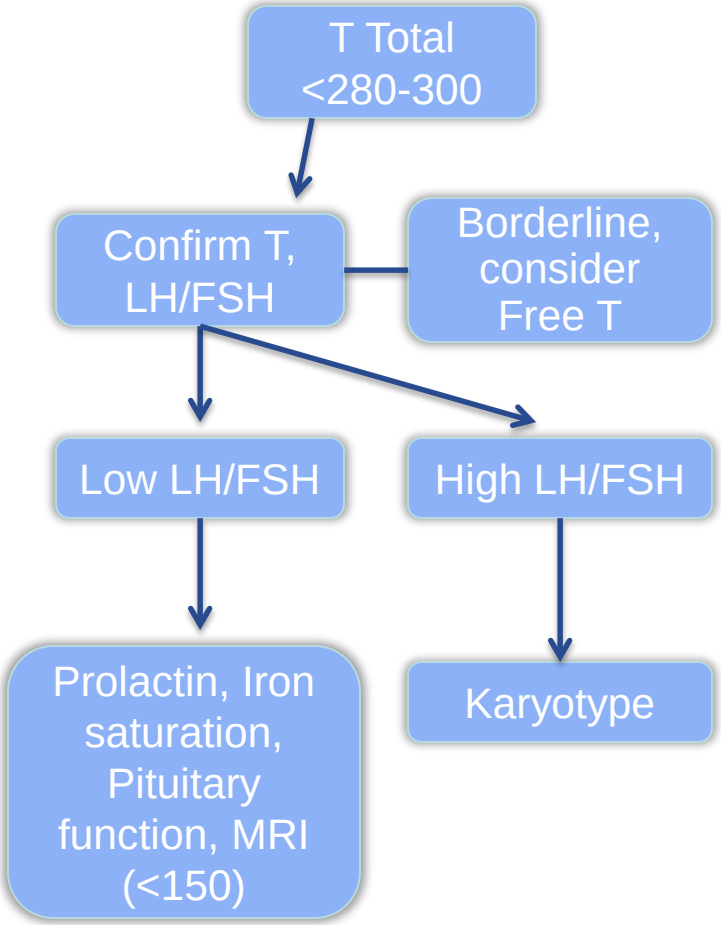
Further Workup?

Society Guideline Statements: Symptoms + Low T

ISA, ISSAM, EAU, EAA, ASA[1-2]



Endocrine Society[3]



1. Wang C. *et al.*/2015 Aging Male.
2. Dohle G. *et al.*/2015 EAU
3. Bhasin S. *et al.*/2010 J Clin Endocrinol Metab.

Case #1

Endocrine Workup

- Repeat AM Total and Free Testosterone
- LH
- CBC

Other Tests to Consider

- Prolactin
- Estrogen
- DEXA Scan
- Semen Analysis

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Case #1

Further Workup Reveals

- Repeat Total Testosterone = 215
- Free Testosterone = 4.5
- CBC and LH normal

Case #1

Decision is made to provide Testosterone

- What form and dose do you prefer for this patient?
- What are your target levels?
- When do you see them back for their first follow-up check?

Case #1

2 years down the road:

- ED has improved
- PSA is rising
  - 1.9 at diagnosis
  - 2.3, 6 months later
  - 2.7, 6 months later
  - 3.5, 6 months later
- DRE still negative

Case #1

What would you do?

- Discuss/Recommend Prostate Biopsy?
- Stop Testosterone?
- Defer Biopsy for now and recheck PSA in 3-6 months while continuing TRT?

PSA Monitoring by Guideline

Endocrine Society[3]: Refer to Urology

- Increase PSA >1.4 over 12 months
- PSA velocity >0.4/yr x 2 years
- Abnormal DRE
- AUASS >19

ISA, ISSAM, EAU, EAA, ASA[1-2]

- “increased” PSA, then biopsy

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Case #1

Post-Biopsy Follow up:

- Pathology:
  - Gleason 3+4=7, 4/12 cores, bilateral
- Patient: “I read that testosterone is like fuel on a fire in men with prostate cancer”

Case #1

Is this patient's prostate cancer a coincidental finding or result of TRT?

Case #1

Follow up:

- TRT stopped
- s/p RALP + PLND
- Pathology
  - pT2c, Gleason 3+4=7
  - LN's/margins negative
- 6 months post-op:
  - No leakage
  - PSA undetectable
  - No erections, TT 180, miserable

TRT Post-Prostatectomy?

- Would you offer this patient TRT?
- Does disease stage, grade, pre-operative PSA, etc. influence this decision?
- How long do you wait to start TRT?
- Would you offer the same recommendations after radiation?

TRT and Active Surveillance for Prostate Cancer?

Had this patient's initial pathology been appropriate for active surveillance, would you offer TRT?

Case#1: TRT and Prostate Cancer Summary

De Novo Prostate Cancer

- x2 meta-analyses demonstrate NO increased risk with TRT[4-5]

Locally advanced or metastatic disease

- TRT is contraindicated

Successfully treated or surveyed localized prostate cancer

- Saturation hypothesis suggests safe[6]
- Retrospective data – no increased risk[7-8]
- 85,862 patients required for RCT

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4. Calof O. *et al.*/2005 J Gerontol A Biol Sci Med Sci
5. Fernandez-Balsells M *et al.*/2010 J Clin Endocrinol Metab
6. Morgentaler A *et al.*/2009 Eur Urol.
7. Pastuszak A *et al.*/2015 J Urol
8. Pastuszak A *et al.*/2015 J Urol

Case #2

Testosterone Replacement and Cardiovascular Risk

Case #2

History:

- 68 yo male, ED and low libido for 3 years
- ED improved with PDE5i's, but low libido persists
- PMH: Obesity, T2DM, HTN, HLD, CAD
  (NSTEMI in 2013, s/p stent x2)
- Meds: ASA, plavix, insulin, metformin, HCTZ, lisinopril, metoprolol, simvastatin
- Normal stress test in the past 6 months for outpatient surgery which went well

Case #2

PE:

- VS normal, obese/BMI 42, DRE unremarkable

Labs:

- HbA1c: 9.7
- Total T 241, repeat 262
  - » Free T 8.5
- PSA 1.4
- LH 5.4, Prolactin 6.6
- Normal Cholesterol Panel

Case #2

For the Audience:

Would anyone start this patient on TRT?

Case #2

Patient is interested in learning about testosterone replacement but says:

"Doc I heard a lawyer on TV say that testosterone causes heart attacks, do you think testosterone is safe for me?"

TRT and Cardiovascular Risk

Low testosterone levels correlate with worsening of cardiovascular risk factors

- Cardiovascular physiology
  - » Carotid intimal medial thickness[9]
  - » C-reactive protein[10]
- Cardiovascular co-morbidities[11]
  - » Diabetes, Obesity, Hyperlipidemia

TRT has no effect/improves CVD and CVD-risk factors

- Several large observational data – improve CVD
- 3 meta-analyses – no change in CVD risk with TRT[12]

TRT can improve overall mortality in older men

- 2, large retrospective series[13-14]
- Men were diagnosed, treated and followed according to guideline recommendations

9. Svartberg J *et al.*/2006 J Intern Med
10. Kaplan S *et al.*/2010 Aging Male
11. Kupelian V *et al.*/2006 J Clin Endocrinol Metab
9. Carson C *et al.*/2012 J Sex Med
10. Muraleedharan V *et al.*/2013 Eur J Endocrinol
11. Shores M *et al.*/2012 J Cin Endocrinol Metab

TRT and Cardiovascular Risk

TRT can worsen CVD risk and mortality

- 5 recent, retrospective studies
  - Basaria *et al.*/2010
  - Vigen *et al.*/2013
  - Xu *et al.*/2013
  - Finkle *et al.*/2014
  - Layton *et al.*/2015
- All relatively weakly design, heterogeneous populations, significant bias

Normalization of T levels improve CV risk and mortality

- Sharma *et al.*/2015[15]
  - » Large (83,000 Veterans), retrospective study
  - » TRT/normalized T levels vs. untreated controls
  - » Decrease in all-cause mortality, MI, and CVA risk at 4.5 yr in TRT treated group

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15. Sharma R, *et al.* Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. Eur Heart J 2015

TRT and Cardiovascular Risk

March, 2015: FDA issues new warning for possible increased risk of MI or CVA with TRT

- "Signal for cardiovascular risk is weak, but only RCT's will determine if testosterone causes CV harm"
- "The benefit and safety of testosterone has not been established for the treatment of hypogonadism due to aging"

TRT and Cardiovascular Risk

Sept, 2015: AACE releases position statement

- "There is no compelling evidence that TRT either increases or decreases CV risk"
- "Men with unequivocally low testosterone after a thorough work-up should be considered for TRT"
- "Extra caution should be exercised in treating the frail elderly"

Case #2:
TRT and Cardiovascular Risk

Given the controversy, what extent of cardiovascular history do you consider safe for TRT?

Would you start this patient on TRT?

What type of TRT would you choose?

What is your therapeutic target?

Case #2: TRT and Cardiovascular Risk

Is there any reason to believe SERMs or AIs present a different risk profile than TRT?

Case #3

Performance Enhancing Drugs / Exogenous Testosterone use and Infertility

Case #3

History:

- 32 yo male
- New c/o low libido, fatigue, and depressed mood during the past 3 months
- PMH/Meds: None reported
- Has children from a prior marriage, but has a new partner and desires more children
- He denies use of PEDs

Case #3

PE:

- Muscular, tan-skinned male, bilateral 10 cc testes, otherwise normal exam

Labs:

- Total T 109, repeat 112
- LH 0.3
- FSH 0.2
- Prolactin normal

Anabolic Steroids & Hypogonadism

Testosterone/AAS suppress the HPG axis, leading to hypogonadism/infertility

- Testosterone contraception data suggest the effect is reversible with cessation[16]
    - o Median recovery time 3-6 mo.
        - Probability estimates 67, 90, 96, 100% by 2 yrs.
    - o Generalizability issues

16. Liu P, *et al.* Rate, extent, and modifiers of spermatogenic recovery after hormonal male contraception: an integrated analysis. Lancet 2006

Anabolic Steroids & Hypogonadism

Anabolic Steroid Induced Hypogonadism (ASIH)

- Same HPG suppression as with TRT induced hypogonadism/infertility
- Several case series suggest reversibility may not be spontaneous[17-18]
- Limited data on treatment options[19]

17. Coward RM, *et al.* Anabolic steroid induced hypogonadism in young men. J Urol 2013
18. Jarow J, Lipshultz LI. Anabolic steroid-induced hypogonadotropic hypogonadism. Am J Sports Med 1990
19. Wenker E, *et al.* The use of HCG-based combination therapy for recovery of spermatogenesis after testosterone use. J Sex Med 2015

Case 3: Anabolic Steroids & Hypogonadism

Would you order any additional tests?

Case 3: Anabolic Steroids & Hypogonadism

Treatment Options:

- TRT + HCG
- HCG +/- FSH
- SERMs/AIs +/- HCG

How do you decide?

Case 3: Anabolic Steroids & Hypogonadism

Is the goal of treatment lifelong or temporary restoration in this patient population?

Thank You!

References

1. Wang C, *et al.* Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. Aging Male 2015 30:1-9.
2. Dohle G, *et al*. Guidelines on Male Hypogonadism. Arnhem: European Association of Urology. 2015.
3. Bhasin S, *et al*. Testosterone therapy in men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2010 95:2536-2559.
4. Calof O, *et al.* Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A Biol Sci Med Sci 2005 60:1451-1457.
5. Fernandez-Balsells MM, *et al.* Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2010 95:2560-75.
6. Morgentaler A, *et al.* Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. Eur Urol 2009 55:310-320.
7. Pastuszak AW, *et al.* Testosterone therapy after radiation therapy for low, intermediate and high risk prostate cancer. J Urol. 2015 194:1271-6.
8. Pastuszak AW, *et al.* Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. J Urol. 2015 190:639-44.
9. Svartberg J, *et al.* Low testosterone levels are associated with carotid atherosclerosis in men. J Intern Med. 2006 259:576-582.
10. Kaplan SA, *et al.* Elevated high sensitivity C-reactive protein levels in aging men with low testosterone. Aging Male. 2010 13:108-112.
11. Kupelian V, *et al.* Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the metabolic syndrome in non0bese men. J Clin Endocrinol Metab. 2006 91:843-850.
12. Carson CC, *et al*. Exogenous testosterone, elderly men: a review of trial data. J Sex Med 2012 9:54-67.
13. Muraleedharan V, *et al.* Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol 2013 169:725-733.
14. Shores MM, *et al.* Testosterone treatment and mortality in men with low testosterone levels. J Cin Endocrinol Metab 2012 97:2050-2058.
15. Sharma R, *et al.* Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. Eur Heart J. 2015 36:2706-2715.
16. Liu PY, *et al.* Rate, extent, and modifiers of spermatogenic recovery after hormonal male contraception: an integrated analysis. Lancet 2006 29:1412-20.
17. Coward RM, *et al.* Anabolic steroid induced hypogonadism in young men. J Urol. 2013 190:2200-5.
18. Jarow JP, Lipshultz LI. Anabolic steroid-induced hypogonadotropic hypogonadism. Am J Sports Med. 1990 18:429-31.
19. Wenker EP, *et al.* The use of HCG-based combination therapy for recovery of spermatogenesis after testosterone use. J Sex Med 2015 12:1334-7.