BALANCING THE RISKS AND BENEFITS OF TESTOSTERONE REPLACEMENT

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Background- Scope of the Problem

- Testosterone testing and prescriptions have nearly tripled in recent years.
- Studies suggest many who receive testosterone (T)therapy do not have their testosterone tested prior to therapy.
- Over 50% do not have testosterone tested after initiation of therapy.
- One third of men who are placed on testosterone therapy do not meet criteria for T deficiency but many men who would benefit from therapy who fail to receive it because of faulty criteria.

Prevalence of Laboratory Testosterone Deficiency

- Difficult to obtain from literature because studies used different cut-off levels for low T and many relied on one serum level.
- All four cited studies in guideline statements showed increasing prevalence levels with increasing age.
- In study using more than one draw in 890 men (low T defined ,325 ng/dL) rates were 12% in 50-59 yrs, 19% in 60-69 yrs, 28% in 70-79 yrs, and 49% in men over 80 years.
- In European Male Aging Study in 3219 men with age range 40-76 (low T defined <317 ng/dL) over all rate was only 2.1%- one draw before 10 a.m.

2018 AUA Guideline for Evaluation and Management of Testosterone Deficiency Multidisplinary Panel

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- Ronald W Lewis- vice chairman
- Landon W. Trost
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Available on AUA website - summary published in J Urol , August 200: 423-32,2018.

Balancing the Risks and Benefits of Testosterone Replacement

- Role of Guidelines in this quest.
- This talk mainly will discuss this topic in relationship to AUA and Canadian Men's Health Foundation published guidelines.
- In AUA guideline each statement (1-31) given a recommendation score with strong indicating net benefit or harm substantial and moderate indicating net benefit or harm moderate. Conditional recommendation (4/31) meant no apparent net benefit or harm.

Balancing the Risks and Benefits of Testosterone Replacement

- In AUA guideline also evidence strength was assigned an evidence strength score from A to C with first two indicating net benefit (or harm) is substantial and C indicating net benefit (or harm) appears substantial.
- Two other terms were used for statement classification , if failing to meet recommendation or evidence strength, and those were Clinical Principal (2/31)or Expert Opinion (4/31).

AUA Guideline development based on strict evidence-based criteria

- 15,217 (from 1/1/1980 to 2/6/2017 original references were evaluated, for unabridged document there are 449/546 references used and summary paper contains 50 selected citations.
- 31 guideline statements for testosterone deficiency were generated, 5 for diagnosis, 7 for adjunctive testing, 9 for patient counseling regarding treatment, 7 for treatment, and 3 for Tx f/u.

Balancing the Risks and Benefits of Testosterone Replacement

- In Canadian publication strength of recommendation 24) was strong ("we recommend"- 14/24) or weak ("we suggest"- 10/24) and quality of evidence relied on appraisal of the likelihood that additional research would modify a recommendation with ratings from very low, low, moderate, or high quality.

Morales A, Bebb RA, Manjoo P, et al. Diagnosis and management of testosterone deficiency syndrome in men: clinical practice guideline. Canadian Medical Journal 187:1369-1377, 2015.

Laboratory Diagnosis of Testosterone Deficiency

- 1. Clinicians should use a total testosterone below 300 ng/dL as a cut off in support of low testosterone. (Moderate, B)
- 2. Diagnosis should be made for low T only after two separate occasions on samples obtained in an early morning draw- before 11 a.m. (Strong, A) - preferably same method and same lab. Diurnal variation with lower amplitudes occur even in elderly. Most urologist don't follow early am draw.

Personal caveat- if first level is low normal then I will obtain total T along with sex hormone binding globulin, and serum albumin to look at calculated free T (http://www.issam.ch/freetesto.htm), <9 pg/mL.

Current Controversy of Total T vs Free T as more Accurate Laboratory Diagnosis of Deficiency

- There is peer review literature supporting either side but AUA committee felt not enough evidence to support free T as dominant method.
- Other quideline published statements support using either total T or free T.
- Canadian quideline favor using free T only in those with symptoms of testosterone deficiency and equivocally low total T levels.

Testosterone Laboratory Measurement

- Free testosterone can only be accurately measured by equilibrium dialysis which is the gold standard- very labor intensive and not generally available.
- Calculated methods using total T, serum albumin, and sex hormone binding globulin are used by most for free T determination.
- Bioavailable Testosterone can be determined by ammonium sulfate precipitation but are technically challenging and time/labor intensive.

Diagnosis of Testosterone Deficiency

- 3. Clincal diagnosis of T deficiency should be made only when patients with low T levels combined with signs and/or symptoms. (Moderate, B)
  Such symptoms include reduced energy, reduced endurance, diminished work and/or physical performance, fatigue, visual field changes (bitemporal hemianopsia), anosmia, depression, reduced motivation, poor concentration, impaired memory, irritability, infertility, reduced sex drive and change in erectile function.
  Signs include:poor virilization, loss of body hair, increase body mass or increased waist circumference, gynecomastia, decrease in testicular size, or varicocele.

Caveat Literature Citation for T level indicatiing low T and symptoms of importance

- European Male Aging Study used cut-off level of <317 ng/dL in a study of 3,219 men from 40-79 years of age to define low T and found sexual symptoms of decreased frequency of morning erections, decreased frequency of sexual thoughts, and erectile dysfunction most correlated with low T. Also some association with inability to perform vigorous activity and psychological symptoms such as loss of energy, sadness and fatigue was associated with low T especially the latter.

  Wu FC et al, N Engl J Med, 2010; 363(2): 123-135.

Diagnosis of Testosterone Deficiency

- 4. Clinicians should consider measuring total testosterone in patients with a history of unexplained anemia, bone density loss, diabetes, exposure to chemotherapy, exposure to testicular radiation, HIV/AIDS, chronic narcotic use, male infertility, pituitary dysfunction and chronic corticosteroid use even in the absence of symptoms or signs listed in guideline 3. (Moderate, B)

Diagnosis of Testosterone Deficiency

- 5. The use of validated questionnaires is not currently recommended to define which patients are candidates for T therapy or monitor symptom response to patients on T therapy. (Conditional , C)
- Canadian guideline publication agrees with strong recommendation and moderate quality evidence.

Adjunctive Testing-Testosterone Deficiency

- 6.In patients with low testosterone clinicians should measure serum luteinizing hormone (LH). (Strong, A)
- 7.Serum Prolactin should be measured in patients with low testosterone (particularly very low levels) levels combined with low or low/normal LH levels. (Strong, A)- also those with symptoms of pituitary disorders. Must be repeated to verify. Men with total T <150 ng/dL in combination with low or low/normal LH should undergo pituitary MRI evaluation.
  Personal caveat. I usually obtain LH and Prolactin level when indicated with second draw for total T.

Adjunctive Testing-Testosterone Deficiency

- 8.Patients with persistently high prolactin levels of unknown etiology should undergo evaluation for endocrine disorders. (Strong,A)
- 9. Serum estradiol should be measured in testosterone deficient patients who present with breast symptoms or gynecomastia prior to commencement of T therapy. (Expert Opinion)
- 10. Men with testosterone deficiency who are interested in fertility should have a reproductive health evaluation prior to tx. (Moderate, B)

Adjunctive Testing-Testosterone Deficiency

- 11. Prior to offering testosterone therapy, clinicians should measure hemoglobin and hematocrit and inform patients regarding the increased risk of polycythemia. (Strong, A)
- 12. PSA should be measured in men over 40 years of age prior to commencement of testosterone therapy to help exclude a prostate cancer diagnosis and serve as baseline for following PSA while on therapy. (Clinical Principle)
- Caveat- I get CBC and PSA with second draw for total T. If baseline Hct is >50% hold T until etiology established. I get f/u Hct and Hgb first three months after commencement, then periodically, at least q 12 months. PSA at 3 months after commencement and then yearly.

Counseling Regarding Treatment of Testosterone Deficiency

- 13. Clinicians should inform testosterone deficient patients that low T is a risk factor for cardiovascular disease (increased risk for major adverse cardiac events such as MI, stroke and possible cardiovascular-relaled mortality). (Strong, B) These patients should be assessed for ASCVD risk factors both fixed (e.g. older age, male gender) and modifiable (e.g. dyslipidemia, hypertension, diabetes, and current cigarette smoking.

Counseling Regarding Treatment of Testosterone Deficiency

- 14. Patients should be informed that T therapy many result in improvements in erectile function, low sex drive, anemia, bone mineral density, lean body mass, and/or depressive symptoms. (Moderate, B)
- 15. Patients should be informed that the evidence is inconclusive whether T therapy improves cognitive function, measures of diabetes, energy, fatigue, lipid profiles and quality of life measures. (Moderate, B)

Counseling Regarding Treatment of Testosterone Deficiency

- 16. The long-term impact of exogenous testosterone on spermatogenesis should be discussed with patients who are interested in future fertility. (Strong, A)
- 17. Clinicians should inform patients of the absence of evidence linking testosterone therapy to the development of prostate cancer. (Strong, B)
- 18. Patients with testosterone deficiency and a history of prostate cancer should be informed that there is inadequate evidence to quantify the risk-benefit ratio of T therapy. (Expert Opinion) Caveat- if treated may want to monitor PSA more frequently- I prefer every 3 months.

Counseling Regarding Treatment of Testosterone Deficiency

- 19. Patients should be informed that there is no evidence linking T therapy to a higher incidence of venothrombolic events. (Moderate, C)
- 20. **Prior to initiating treatment, clinicians should counsel patients that, at this time, it cannot be stated definitely whether T therapy increases or decreases the risk of cardiovascular events. (Moderate, B)**
  Despite FDA labeling instructions to manufacturers.

Testosterone Therapy and Cardiovascular Disease

- Random Clinical trials have failed to categorically define if T therapy increases the incidence of MACE when compared to placebo.
- Thresholds for low T were not universal, characteristics of treated versus placebo populations were present,inconsistent defined endpoints to categorize severe cardiac events, duration of follow-up varied widely, many trials not powered to detect cardiac events as primary outcomes but were catalogued as adverse outcomes.

Testosterone Therapy and Cardiovascular Disease

- 24. Testosterone therapy should not be commenced for a period of three to six months in patients with a recent history of cardiovascular events. (Expert Opinion)

Treatment of Testosterone Deficiency

- 22. Clinicians should adjust T therapy dosing to achieve a total T level in the middle tertile of the normal reference range (450-600 ng/dL). (Conditional, C)
- 23. Exogenous T therapy should not be prescribed to men who are currently trying to conceive. (Strong, A)

Treatment of Testosterone Deficiency

- 25. Clinicians should not prescribe alkylated oral testosterone. (Moderate, B)
- 26. Clinicians should discuss the risk of transference with patients using testosterone gels/creams. (Strong, A)

Follow up of Men on Testosterone Therapy

- 29. Clinicians should measure an initial follow-up total T level after an appropriate interval to ensure that target testosterone levels have been achieved. (Expert Opinion) For those on topical gels, patches, and intranasal formulations first T should be measured 2-4 weeks after commencement of therapy; for those on agents to stimulate natural pituitary hormones measure T no sooner than four weeks after commencement; for those receiving short term IM or sub-Q measure no sooner than three to four cycles; for long acting IM measure in mid cycle at about 5 weeks; for sub-q pellets measure 2- 4 weeks after commencement and then after q 10-12 weeks.

Therapeutic Agents for Treatment of Testosterone Deficiency

- Transdermal agents- gels and solutions
- Transdermal agents- patches
- Buccal agents
- Intranasal gel
- Injectable agents- short acting
- Injectable agents- long acting
- Subcutaneous pellets

Risk Benefit Considerations for Exogenous Testosterone Therapy

- Differences exist for peak and trough levels provided by exogenous agents- is variation from normal diurnal variation important or perhaps better for those treatments which vary this normal diurnal variation.
- Side effects for long term use of testosterone therapy need to be better studied. There is a great variation in method of delivery between therapeutic choices.
- Some agents are at higher risk for increasing Hct/Hgb levels, decreasing gonadotropins, increase in estrogen.
- There is a need for head to head studies to address points above.

Testosterone Deficiency

- Less evidence for benefit versus risk for following slides

Counseling Regarding Treatment of Testosterone Deficiency

- 21. All men with testosterone deficiency should be counseled regarding lifestyle modification *as a treatment strategy. (Conditional, B) *losing weight, increasing physical activity.

Treatment of Testosterone Deficiency

- 27. Clinicians may use aromatase inhibiters, human chorionic gonadotropin, selective estrogen receptor modulators, or a combination thereof in men with testosterone deficiency desiring to maintain fertility. (Conditional, C) Personal caveat I prefer the use of Clomipene (SERM) 50 mg three times a week.

Treatment of Testosterone Deficiency

- 28. Commercially manufactured testosterone products should be prescribed rather than compounded testosterone, when possible. (Conditional, C)

Follow up of Men on Testosterone Therapy

- 30. Testosterone levels should be measured every 6-12 months while on testosterone therapy. (Expert Opinion)
- 31. Clinicians should discuss cessation of testosterone therapy three to six months after commencement of treatment in patients who experience normalization of total testosterone levels but fail to achieve symptom or sign improvement. (Clinical Principal)