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Lesson 26 Volume 39

A Critical Appraisal of the AUA Evaluation and Management of Testosterone Guidelines*

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to critically evaluate the individual components of the AUA Evaluation and Management of Testosterone Guidelines and apply their use in clinical practice.

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INTRODUCTION

Testosterone therapy was approved by the U.S. Food and Drug Administration more than 50 years ago. Recent decades have seen a dramatic increase in the diagnosis and treatment of testosterone deficiency. While a variety of societies have previously made recommendations regarding testosterone deficiency in men, the American Urological Association released the first guidelines in 2018.

The guidelines committee underwent a keyword based literature search of articles published between January 1, 1980 and February 6, 2017. Articles were reviewed for sufficient evidence, and the committee crafted 31 statements that broke down into 5 categories (diagnosis, adjunctive testing, counseling regarding treatment, treatment and follow-up). When adequate evidence existed for a guideline, it was assigned a strength per the AUA methodology for guidelines of A (high), B (moderate) or C (low), with an accompanying support of strong, moderate or conditional recommendation. If published evidence to support a guideline did not exist, the guideline could be considered a "clinical principle" or "expert opinion."

DIAGNOSIS OF TESTOSTERONE DEFICIENCY

Guideline statement 1. Clinicians should use a total testosterone level below 300 ng/dl as a reasonable cutoff in support of the diagnosis of low testosterone. (Moderate Recommendation; Evidence Level: Grade B)

Commentary: Several laboratory cutoffs have been endorsed. **Picking a dichotomous cutoff begs the question of balancing sensitivity with specificity since using a lower laboratory value will ensure sensitivity of the testing by capturing any possible patient but will lower specificity of the testing to the point of uselessness**. A laboratory value based on a pathophysiological principle (eg testosterone receptor saturation) would be ideal but has not yet been identified. The guidelines panel focused on a series of RCTs where TT was evaluated to determine this value. In all of these studies TT <350 ng/dl was used as an inclusion criterion.

Cutoffs of 231–300 ng/dl have been used by the Endocrine Society, European Association of Urology and the International Society for Sexual Medicine.[1-3] Our best understanding of symptom clustering with laboratory values was elucidated from the EMAS (European Male Ageing Study) group. A random population of more than 3000 men from 8 European centers were surveyed and it was found that 3 sexual symptoms and limited physical vigor were most predictably tied to testosterone levels.[4] Different thresholds were identified for decreased sexual thoughts (230 ng/dl), erectile dysfunction (250 ng/dl), decreased morning erections (320 ng/dl) and diminished vigor (370 ng/dl). Interestingly a survey of members of the Sexual Medicine Society of North America revealed that most practitioners used a cutoff of 300 ng/dl; however, 31% still considered TT in symptomatic men with normal levels.[5]

Guideline statement 2. The diagnosis of low testosterone should be made only after 2 total testosterone measurements are taken on separate occasions with both conducted in an early morning fashion. (Strong Recommendation; Evidence Level: Grade A)

Commentary: A standardized approach is certainly required. While older men have a less pronounced diurnal variation than younger men,[6-8] a standardized approach with morning draw is still recommended.

Guideline statement 3. The clinical diagnosis of testosterone deficiency is only made when patients have low total testosterone levels combined with symptoms and/or signs. (Moderate Recommendation; Evidence Level: Grade B)

Commentary: The crux of this statement is that a low laboratory value alone does not verify TD largely related to the nonspecificity of symptoms. For example sexual symptoms could be related to intimacy issues, sexual function problems or general health problems. In the guidelines there is no specific mention of an exact number of symptoms that would clearly define TD; however, other works have indicated that the greater the number of symptoms, the higher the probability that one has TD.[9]

Guideline statement 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 associated with TD. (Moderate Recommendation; Evidence Level: Grade B)

Commentary: The recommendation for screening, even without acknowledged symptoms of TD, is interesting and indicates that certain conditions ("signs") may increase the risk of TD. Routine screening of these groups may yield men who would benefit from TT even without symptoms. However, improvements in disease specific outcomes, and overall health, with TT are either modest or unproven.

Guideline statement 5. Use of validated questionnaires is not currently recommended either to define which patients are candidates for testosterone therapy or to monitor symptom response in patients on testosterone therapy. (Conditional Recommendation; Evidence Level: Grade C)

Commentary: A variety of recognized tools, including the ADAM (Androgen Deficiency in the Aging Male) questionnaire, AMS (Aging Male Symptoms) scale and the MMAS (Massachusetts Male Aging Study) questionnaire, have been used in studies. And while their sensitivities are 97%, 83% and

ABBREVIATIONS: AI (aromatase inhibitor), AUA (American Urological Association), BMI (body mass index), CVD (cardiovascular disease), ED (erectile dysfunction), FDA (U. S. Food and Drug Administration), hCG (human chorionic gonadotropin), LH (luteinizing hormone), MRI (magnetic resonance imaging), PSA (prostate specific antigen), RCT (randomized controlled trial), SERM (selective estrogen receptor modulator), TD (testosterone deficiency), TT (testosterone therapy), VTE (venothrombolic events)

60%, respectively, their specificities are 30%, 59% and 39%.[10] As the reader can see, these commonly used questionnaires have relatively low specificity for diagnosis, and with the generally higher sensitivities they would serve better as screening questionnaires. Additionally these questionnaires have not been validated for longitudinal use to follow a cohort over time or to monitor response to treatment.

ADJUNCTIVE TESTING

Guideline statement 6. In patients with low testosterone clinicians should measure serum luteinizing hormone levels. (Strong Recommendation; Evidence Level: Grade A)

Commentary: **LH is important for accurate determination of primary vs secondary TD and has value with regard to treatment options.** A normal LH value with low testosterone implies secondary TD and should prompt consideration of the hypothalamic-pituitary axis.

While no explicit value of LH is defined as abnormal by the guidelines panel, a higher value has previously predicted a poor response to selective estrogen receptor modulators as a treatment option.[11] The mechanism of action of SERMs is to increase endogenous LH by blocking estradiol feedback centrally. These medications are considered "off label" for the treatment of TD as they were originally approved by the FDA for other indications. While TT often requires transdermal or injectable routes, SERMs have the convenience of oral dosing. Additionally these are not considered controlled substances in many states, making prescribing more convenient for providers. Reasonable long-term outcomes have been established with regard to efficacy.[12]

Guideline statement 7. Serum prolactin should be measured in patients with low testosterone levels combined with low or low normal luteinizing hormone levels. (Strong Recommendation; Evidence Level: Grade A)

Guideline statement 8. Patients with persistently high prolactin levels of unknown etiology should undergo evaluation for endocrine disorders. (Strong Recommendation; Evidence Level: Grade A)

Commentary: Although prolactinoma is an uncommon cause of TD, the committee makes 2 statements regarding the pituitary and prolactin, and physicians should be cognizant of the possibility of a pituitary tumor causing optic chiasma compression effects. The recommendation of pituitary MRI for levels less than 150 ng/dl even with a normal prolactin level is commensurate with endocrine guidelines.[1]

An argument against routine assessment of prolactin levels and pituitary imaging primarily regards cost-effective care. Pituitary incidentalomas are seen in approximately 20% of the population, and the cost associated with pituitary MRI and pituitary incidentalomas is significant.[13, 14] While routine screening for prolactin levels is inexpensive, routine use of MRI certainly increases the cost. Indeed, the cost of obtaining MRI for all men with a testosterone <150 ng/dl is considerable. One study estimated the incidence of dopamine agonist treated hyperprolactinoma in men to be 1.4 per 100,000 person-years.[15] Routine detection of small and nonfunctional pituitary adenomas has limited clinical utility. Possibly a prolactin threshold to obtain MRI has more value as the guidelines further indicate that prolactin levels correlate with tumor size and that most prolactinomas have a serum prolactin value of at least 250 mg/l.

Guideline statement 9. Serum estradiol should be measured in patients with TD who present with breast symptoms or gynecomastia prior to the commencement of testosterone therapy. (Expert Opinion)

Commentary: Serum estradiol levels have been correlated with bone density outcomes in men, and considering the physiological risk of low bone density in men with TD, routine evaluation and monitoring of estrogen levels should be considered.[16, 17] **Additionally knowledge of estradiol levels may be beneficial in management as an aromatase inhibitor may be preferred over a SERM for men with high estrogen levels or an unfavorable testosterone-to-estrogen level (less than 10:1).** AIs principally decrease peripheral aromatization of testosterone to estrogen, thus raising testosterone levels.

Guideline statement 10. Men with testosterone deficiency who are interested in fertility should have a reproductive health evaluation performed prior to treatment. (Moderate Recommendation; Evidence Level: Grade B)

Commentary: While the statement itself is open ended, it highlights the need to consider patient goals and comorbid conditions during diagnosis and therapy. Treatment options for men desiring to preserve fertility are more extensively discussed in later sections. Clinicians should consider that they may identify men with undiagnosed conditions (eg Klinefelter syndrome) due to the common overlap of TD and infertility.

Guideline statement 11. Prior to offering testosterone therapy clinicians should measure hemoglobin and hematocrit and inform patients regarding the increased risk of polycythemia. (Strong Recommendation; Evidence Level: Grade A)

Commentary: The concern for polycythemia is that with increased red cell mass there may be issues with deformation of individual cells and the appropriate flow of blood. Short acting injectable preparations appear to have the largest increase in red cell mass; however, this is possible with all forms of TT, including oral restoration options.[18]

An actual threshold at which the hematocrit becomes "dangerous" has not been established. The guidelines recommend maintaining a hematocrit of less than 54%, and other authors recommend not initiating TT in men with a hematocrit greater than 50% until evaluated.[19] **Routine hematology evaluation in patients with a high hematocrit is advisable, especially as these patients will almost certainly end up with a hematocrit over 54% once on treatment and the previous relationship with hematology allows easier access for therapeutic phlebotomy.**

One series demonstrated that the patients in the highest quintile of hematocrit levels had a greater risk of venous thromboembolism (1.5-fold).[20] However, the authors acknowledged that the study did not account for dose dependent effects of smoking. It is certainly plausible that the link between high hematocrit and thromboembolic events was related to comorbid conditions as causality was not established in this study.

Guideline statement 12. PSA should be measured in men over 40 years of age prior to commencement of testosterone therapy to exclude a prostate cancer diagnosis. (Clinical Principle)

Commentary: This is an interesting guideline as routine prostate cancer screening is generally recommended to begin

at age 55 years.[21] The TD guidelines acknowledge that there is no credible evidence linking TT and development of prostate cancer. In men without advanced disease TT has been associated with a lower risk of aggressive cancer and no significantly increased risk of recurrence even in cases managed by radiation with the prostate left in situ.[22, 23]

While one could make a case for not incurring the costs of screening in men younger than 55 years old based on the above rationale, this is unrealistic due to medicolegal issues. In a relevant and elucidating study of prostate cancer risk in men younger than 50 years old undergoing an aggressive prostate biopsy strategy 19% were diagnosed with prostate cancer and only 51% of those men met criteria for active surveillance.[24] **Of men with Gleason 7 or greater disease all had a PSA above 1.5 ng/dl.**

COUNSELING REGARDING TREATMENT OF TESTOSTERONE DEFICIENCY

Guideline statement 13. Clinicians should inform testosterone deficient patients that low testosterone is a risk factor for cardiovascular disease. (Strong Recommendation; Evidence Level: Grade B)

Commentary: **This statement offers urologists the opportunity to counsel men in general of their greater risk of CVD regardless of testosterone status.** Men have been shown to have an overall increase in risk of cardiovascular disease as compared to women; however, the underlying reason behind male gender as an independent risk factor for CVD remains unknown.[25] With regard to TD and CVD several studies have indicated an inverse relationship between testosterone level and CVD risk.[26] The increased risk of CVD seen with androgen deprivation therapy in the treatment of prostate cancer would also suggest a causal relationship. Recent controversy over the association between androgen deprivation therapy and cardiovascular disease based on FDA statements has led to organizations issuing warnings regarding the strong link between low testosterone and cardiovascular events.

It is possible that low testosterone is simply a marker of poor health; however, given the risk of reduced survival and increased morbidity with cardiovascular disease, the significant finding of an increased CVD risk with low testosterone should not be ignored. It is therefore difficult to find fault with this recommendation while the underlying biology of this relationship requires further study.

Guideline statement 14. Patients should be informed that testosterone therapy may result in improvements in erectile function, sex drive, anemia, bone mineral density, lean body mass and/or depressive symptoms. (Moderate Recommendation; Evidence Level: Grade B)

Commentary: **The strength of this recommendation is that it addresses the underlying principle of treating low testosterone only when the patient is symptomatic.** While TT in males with TD and ED has been shown to improve ED, we would be cautious about overemphasizing the potential effect testosterone may have on erectile function.[27] Many men presenting with TD and ED have other comorbidities (eg vascular disease) or etiologies (eg radical pelvic surgery) that may be contributing. Therefore, men presenting with both should be counseled on TT as well as other conventional options cited in the AUA guidelines.[28]

Improvements in libido, bone mineral density and depressive symptoms are well documented in the literature, including data from recent RCTs.[29-32] We would caution clinicians on counseling patients regarding improved lean body mass as the statistical significance of this improvement in studies remains weak, treatment duration doses vary and, overall, BMI does not change with TT (while lean body mass might). As testosterone is anabolic, patients would generally be expected to gain rather than lose weight.[33] The underlying contributing factors to a high BMI, similar to ED, are multifactorial and likely require multiple interventions (eg diet and exercise), which should be discussed.

Guideline statement 15. Patients should be informed that the evidence is inconclusive regarding whether testosterone therapy improves cognitive function, measures of diabetes, energy, fatigue, lipid profiles and quality of life measures. (Moderate Recommendation; Evidence Level: Grade B)

Commentary: As highlighted above, a number of conditions that have been targeted to improve with TT are multifactorial and therefore may not improve without other interventions. Although some trials support benefit in the metrics highlighted in guideline statement 15, others do not support efficacy. While this statement acknowledges limitations in the data for TT in these conditions, it does not exclude the clinician from discussing them with the patient. **As suggested by the panel, the clinician should be thoughtful and cautious when presenting potential improvements to the patient, particularly in regard to those conditions with the least supportive data (ie cognitive function, diabetes and lipid profile).** Quality of life measures remain difficult to study due to variability in methodology and inherent bias in patient reported symptoms.

Guideline statement 16. The long-term impact of exogenous testosterone on spermatogenesis should be discussed with patients who are interested in future fertility. (Strong Recommendation; Evidence Level: Grade A)

Commentary: Exogenous testosterone has been tested as a contraceptive as it inhibits spermatogenesis through central suppression of the hypothalamic-pituitary-gonadal axis. **Therefore, TT can lead to infertility even in males with hypogonadotropism.**[34] The return of successful spermatogenesis after cessation of exogenous testosterone can take up to 2 years, although the majority of patients recover function within a year. **However, there is a subset of men who may never have return of spermatogenesis, which highlights the importance of this strong recommendation.** This is a particularly important statement in light of prior survey results demonstrating that 25% of urologists would treat infertile males with exogenous testosterone.[35]

The panel suggests in their discussion that special attention be given to men with Klinefelter syndrome (47,XXY). Many of these patients receive testosterone supplementation at puberty if their testosterone levels are low or low normal to assist in development and treat the symptoms of low testosterone. Indeed, patients with Klinefelter syndrome require special attention with regard to this guideline statement as the majority will require surgical sperm retrieval and assisted reproduction (eg in vitro fertilization). Therefore, it is recommended that these patients be managed by a multidisciplinary team of endocrinologists and urologists with experience in treating

Klinefelter syndrome or specially trained andrologists.

Guideline statement 17. Clinicians should inform patients of the absence of evidence linking testosterone therapy to the development of prostate cancer. (Strong Recommendation; Evidence Level: Grade B)

Commentary: The importance of this guideline statement cannot be overemphasized as there has been a perception among the medical community that TT increases the risk of prostate cancer ever since the Nobel Prize was awarded to Huggins and Hodges in 1966 for the discovery that androgen deprivation is an effective treatment for metastatic prostate cancer.[36] While PSA levels may increase after initiation of TT, there is no long-term evidence that links TT to development of prostate cancer despite the FDA's warning. **As noted by Salter and Mulhall, a review of all major international guidelines on TT showed a consensus that there is no evidence testosterone therapy causes prostate cancer.[37]** As such, it is difficult to take issue with this recommendation.

Guideline statement 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 testosterone therapy. (Expert Opinion)

Commentary: While there are several studies examining the use of TT in men undergoing active surveillance or who have been treated for prostate cancer, the strength of the data remains limited as most series have short follow-up, have modest numbers of patients or are retrospective in nature. As such, drawing definitive conclusions is difficult. Unfortunately as the diagnosis of TD becomes more common and screening for prostate cancer continues, these 2 conditions will increasingly overlap. There is fear that TT will increase prostate cancer progression, biochemical recurrence or metastasis. Much of this fear is based on findings that androgen deprivation inhibits prostate cancer and the assumption that the converse must also be true. However, the androgen receptor saturation model suggests that after a certain threshold (likely <200 ng/dl) prostate cancer cells will no longer respond to an increase in level of testosterone.

This guideline statement therefore offers the clinician the opportunity to have an informed discussion with the patient and make a shared decision. While clinicians may be more comfortable initiating TT in surgically or radiation treated individuals, a gray zone exists for those with low risk disease and stable PSA, including those with a history of locally advanced or high risk disease. Until more definitive randomized, placebo controlled trials are available this will remain true and the choice to initiate treatment will be individualized.

Guideline statement 19. Patients should be informed that there is no definitive evidence linking testosterone therapy to a higher incidence of venothrombolic events. (Moderate Recommendation; Evidence Level: Grade C)

Commentary: Like many discussions concerning the risks of testosterone therapy highlighted in this critical review, whether the risk of VTE should stop an individual from starting replacement therapy is shared decision making. As noted within the guideline statement discussion, the data surrounding the FDA warning are predominantly anecdotal. However, there exists one retrospective study that suggests the rate of VTE is higher in the first 6 months of therapy compared to base rate. Importantly, the association is lost after the first 6 months.[38] Additionally, and more recently, an analysis of private commercial insurance claims suggested that in hypogonadal men treated with testosterone there were increased odds of VTE, particularly in those younger than 65 years old.[39] However, this is in contrast to 2 prospective studies and 1 retrospective study cited by the authors that showed no increased risk of VTE.

As the data remain conflicting, further prospective studies are needed to better evaluate this potential complication. **However, we believe patients should be informed of this and a shared decision to proceed decided together.**

Guideline statement 20. Prior to initiating treatment clinicians should counsel patients that, at this time, it cannot be stated definitively whether testosterone therapy increases or decreases the risk of cardiovascular events (eg myocardial infarction, stroke, cardiovascular related death and all cause mortality). (Moderate Recommendation; Evidence Level: Grade B)

Commentary: This guideline statement highlights the controversy surrounding TT with regard to major adverse cardiac events. As discussed in the commentary for guideline statement 13, TD may increase the risk of CVD. As such, one would suppose that TT may reverse this risk. However, this has not been shown conclusively in the literature. As the guidelines highlight, there have been several studies, including randomized, placebo controlled trials, that have conflicting results regarding major adverse cardiac events. Most patients should be informed about the presence of conflicting literature before proceeding with TT. **However, given these data, individuals who certainly require caution are those with a history of cardiovascular disease.**

Guideline statement 21. All men with testosterone deficiency should be counseled regarding lifestyle modifications as a treatment strategy. (Conditional Recommendation; Evidence Level: Grade B)

Commentary: As mentioned in the commentary for guideline statement 14, the goal of testosterone therapy is to treat symptomatic TD. Addressing these comorbidities and symptoms may require a multifactorial approach, including lifestyle modifications. Many of the comorbidities and symptoms associated with TD (as addressed in guideline statements 14 and 15), including high BMI, depression, diabetes and hyperlipidemia, can be addressed with lifestyle modifications such as diet and exercise.[40-44]

It would therefore be beneficial to treat the symptomatic patient with low testosterone using a multifaceted approach by recommending diet and exercise modifications in conjunction with TT for the best results. While the evidence in the literature may be limited or conflicting with regard to these outcomes with TT alone, lifestyle modifications in our population will generally be beneficial for health regardless of TT.

TREATMENT OF TESTOSTERONE DEFICIENCY

Guideline statement 22. Clinicians should adjust testosterone therapy dosing to achieve a total testosterone level in the middle tertile of the normal reference range. (Conditional Recommendation; Evidence Level: Grade C)

Commentary: The panel defines the middle tertile of the

physiological range for testosterone as 450–600 ng/dl as this is the middle tertile for most laboratories and it aims to avoid overtreatment. The panel recognizes that individual adjustments may need to be made depending on the age of the patient. **There are no RCTs to support this target range; however, it is difficult to take issue with this recommendation as the goal of treatment is relief of symptoms, and thus restoration of physiological levels represents a logical target.** Supratherapeutic levels as a target likely have no symptomatic benefit and carry an increased risk of adverse effects.[45]

Guideline statement 23. Exogenous testosterone therapy should not be prescribed to men who are currently trying to conceive. (Strong Recommendation; Evidence Level: Grade A)

Commentary: The risk of exogenous testosterone therapy and impaired spermatogenesis has been addressed in the commentary for guideline statement 16.

Guideline statement 24. Testosterone therapy should not be commenced for a period of 3 to 6 months in patients with a history of cardiovascular events. (Expert Opinion)

Commentary: **As mentioned previously, clinicians should proceed with caution in initiating testosterone therapy in any patient with preexisting cardiac disease.** Given the relatively short period of up to 6 months proposed by the panel and the non-immediate life-threatening nature of low testosterone, it is reasonable to temper the urgency of initiating therapy prior to 6 months.

Guideline statement 25. Clinicians should not prescribe alkylated oral testosterone. (Moderate Recommendation; Evidence Level: Grade B)

Commentary: Due to first pass metabolism in the liver, the serum levels of alkylated oral (17α-alkylated) testosterone can vary, and there is a risk of hepatotoxicity including impaired function and hepatic cholestasis.[46] **Given the abundance of other administration options for replacement therapy, it is easy for the clinician to avoid prescribing alkylated oral testosterone.**

Guideline statement 26: Clinicians should discuss the risk of transference with patients using testosterone gels/creams. (Strong Recommendation; Evidence Level: Grade A)

Commentary: There is a wide variety of FDA approved topical testosterone therapies, including gels and solutions. As with any topical application, there is a chance that it could be transferred via direct contact with another individual. While this inherent risk may be relatively inconsequential for cosmetics or sunscreen, transference of a drug containing product may treat a person inadvertently. This is certainly a risk with testosterone containing gels and creams, and, while rare, hyperandrogenism has been documented from transference, with the risk lasting up to 8 hours after application.[47] **While the risk of adverse effects from transference is low, the consequences, such as precocious puberty in children and virilization in women, are unacceptable.**

Guideline statement 27. Clinicians may use AIs, human chorionic gonadotropin, selective estrogen receptor modulators or a combination thereof in men with TD desiring to maintain fertility. (Conditional Recommendation; Evidence Level: Grade C)

Commentary: Given the prevalence of symptomatic low testosterone in men, there are patients who desire both to maintain fertility and treat TD. In this subset of patients treatment with available exogenous testosterone is inappropriate, and therefore stimulation of endogenous production is preferred. The mechanism of SERMs and AIs has been discussed previously. hCG is an LH analogue that stimulates intratesticular testosterone production.

However, treatment with one of the above medication classes requires 2 important assumptions. The first assumption is that the patient has adequate testicular function as both hCG and SERMs (and to some extent AIs) rely on LH to augment intratesticular production. Theoretically stimulation of endogenous production results in adequate serum levels, and men with normal levels of LH are good candidates. The second assumption is that stimulation of endogenous testosterone via these medication classes will lead to clinical results similar to exogenous administration. While this assumption makes physiological sense, there are limited data in the literature to either refute or support it.

The treating clinician should keep in mind several factors before adopting this conditional recommendation. These alternative therapies will have a different side effect profile from exogenous testosterone due to differences in mechanisms of action. Adverse effects range from the bothersome, such as hot flashes (with AIs), to the life-threatening, such as thromboembolism (with tamoxifen). Additionally many exogenous testosterones are low cost, and alternative therapies can be more expensive.[48] Finally, only hCG has been approved by the FDA for treatment of hypogonadotropic TD, while use of other medications is off label. Another potential benefit of these treatments is an increase in semen parameters, which has been suggested in some studies.[49, 50]

Guideline statement 28. Commercially manufactured testosterone products should be prescribed rather than compounded testosterone when possible. (Conditional Recommendation; Evidence Level: Grade C)

Commentary: The benefit of compounded testosterone preparations is the potential for reduced cost as compared to brand name formulations. However, as the panel astutely points out, there can be considerable variation in the amount of active ingredient. **Patients should therefore be cautioned about the inherent limitations of compounding pharmacies and, as they would with any testosterone preparation, be closely monitored for a total testosterone level in the reference range.**

FOLLOW-UP OF MEN ON TESTOSTERONE THERAPY

Guideline statement 29. Clinicians should measure an initial follow-up total testosterone level after an appropriate interval to ensure that target levels have been achieved. (Expert Opinion)

Guideline statement 30. Testosterone levels should be measured every 6–12 months while the patient is on testosterone therapy. (Expert Opinion)

Commentary: Similar to the optimal testosterone level, there are few data to support the optimal schedule for checking total testosterone levels. Therefore, the timing is dictated by the

formulation, given the variation in time that it will take each to achieve the clinician's optimal level. Checking total testosterone within the first few weeks is unlikely to be of clinical benefit as endogenous testosterone may still be present and not yet fully suppressed. In the discussion for this guideline statement the panel suggests a period of 2–4 weeks for gels, patches and intranasal formulations, 4–8 weeks for the short acting intramuscular preparations, mid cycle (around 14 weeks) for long acting intramuscular preparations and 2–4 weeks for subcutaneous pellets (to determine dose/timing). This is similar to laboratory checks of maintenance therapy as no definitive schedule or evidence to support one exists and it is simply based on the pharmacology of the medication and symptoms of the patient. It is difficult to take issue with these guideline statements based on the preparations' pharmacology.

Guideline statement 31. Clinicians should discuss the cessation of testosterone therapy 3 to 6 months after commencement of treatment in patients who experience normalization of total testosterone levels but fail to achieve symptom or sign improvement. (Clinical Principle)

Commentary: As discussed, the goal of treatment of low testosterone is the amelioration of symptoms. Therefore, if treatment is not working despite correction of TD, as this clinical principle addresses, therapy should be stopped. **There currently is insufficient evidence to recommend continuation of therapy despite normalization of testosterone in the absence of symptomatic improvement to address comorbidities such as lipid profiles, diabetes, cognitive function and cardiovascular risk.**

CONCLUSIONS

As TT is increasingly adopted worldwide by numerous clinicians (primary care providers, urologists and endocrinologists) able to care for patients with hypogonadotropism, guidelines have an important role in evidence-based standardization of TD treatment.[51] While the AUA guidelines serve as an outline for the prescribing clinician, there remains a significant amount of controversy within the field, resulting in a number of conditional recommendations and expert opinions.

There are several takeaways from this critical review of the AUA Evaluation and Management of Testosterone Guidelines. First, testosterone therapy should only be prescribed in the setting of documented low testosterone with symptoms. Second, there is insufficient evidence currently to recommend initiating TD therapy solely to reduce the risk of, or treat, conditions such as abnormal lipid profiles, diabetes, cognitive decline and increased BMI. Third, several controversies exist surrounding TT and its potential benefits and risks that patients must be aware of when counseled on starting treatment. One is that patients should be reassured that TT does not increase the risk of prostate cancer. While clinicians and patients should be reassured that treatment of TD in patients with low risk, localized prostate cancer on active surveillance or those previously treated with local therapy appears safe, the data around treatment of high risk or locally advanced disease are unclear at this time. Fourth, patients should be informed about the risk of cardiovascular disease with TD and the potential risk of cardiovascular events in those treated with testosterone. Finally, all men who are considering treatment for TD should also adopt lifestyle changes such as healthy diet and regular exercise in an attempt to obviate the need for TT.

DID YOU KNOW?

- TD is defined by low laboratory values with associated signs or symptoms.
- Laboratory values like PSA, hematocrit, LH, prolactin and estradiol are important for both treatment and screening for related diseases.
- Prior to initiation of TT it is vital to counsel patients regarding their expectations, risks of therapy and the fertility consequences of supplementation. The patient must understand the goal is symptomatic relief with potential improvements in areas such as erectile function, libido, bone density and depressive symptoms, while there remains inconclusive evidence regarding such areas such as cognition and diabetes. Risks must be discussed as detailed in the AUA Evaluation and Management of Testosterone Guidelines. Finally, clinicians must discuss the risk of suppression of spermatogenesis, and males of reproductive age should carefully consider whether they are interested in having children.
- TT does not cause prostate cancer, and the decision to start TT in a patient with active and/or treated prostate cancer requires shared decision making through discussion of risks and benefits as there are currently no definitive trials addressing this topic.
- TT should be stopped if a patient's symptoms are not relieved despite restoration of physiological levels.

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Study Questions Volume 39 Lesson 26

1. A 34-year-old man who is trying to conceive with his partner is started on 25 mg oral clomiphene citrate daily for a testosterone level of 190 ng/dl and low libido. Eight weeks later the patient reports that his wife is pregnant but he notes a further decline in libido. His total testosterone level and LH are now 200 ng/dl and 13.3 IU/l, respectively. The next step is
   a. switch to 500 IU subcutaneous hCG 2 times per week
   b. increase clomiphene dose to 50 mg daily
   c. decrease clomiphene dose to 12.5 mg daily
   d. stop clomiphene

2. A 47-year-old man with chronic back pain, dyslipidemia, erectile dysfunction and type 2 diabetes mellitus is referred to a urologist for treatment of his low testosterone (total testosterone 170 ng/dl). Treatment with replacement testosterone therapy will likely improve his
   a. erectile function
   b. dyslipidemia
   c. back pain
   d. hemoglobin A1c

3. A 54-year-old-man was started on 1% testosterone gel 7 months ago for symptomatic low testosterone with a total testosterone level of 171 ng/dl. His total testosterone level is now 385 ng/dl. He continues to complain of low energy, depression and low libido. The next step is
   a. continue therapy and recheck total testosterone in 6 months
   b. increase application of testosterone gel to twice daily
   c. switch to oral 17α-alkylated testosterone
   d. stop testosterone therapy

4. A 32-year-old man was started on 1% testosterone gel 3 years ago for symptomatic low testosterone by his primary care provider. He has been attempting to conceive with his 35-year-old wife for the past 14 months. His wife had a normal fertility workup by her gynecologist. Semen analysis revealed azoospermia and a seminal volume of 2.3 ml. The next step is
   a. transurethral ultrasound
   b. testicular biopsy
   c. stop testosterone therapy and recheck semen analysis in 4 months
   d. stop testosterone therapy, start hCG and recheck semen analysis in 4 months

5. A 45-year-old man with HIV and type 2 diabetes mellitus has worsening erectile function. He is compliant with all his medications. His most recent viral load is undetectable. He has a new partner with whom he would like to be sexually active and he is interested in taking a phosphodiesterase type 5 inhibitor. The next step in his initial workup is
   a. check hemoglobin A1c
   b. check morning testosterone
   c. check PSA and perform digital rectal examination
   d. refer back to primary care for cardiac workup

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