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Review Article

Risks, Contraindications and Follow up After Testosterone Replacement Therapy: Lack of Consensus among Specialties and Countries

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ABSTRACT

The direct to consumer marketing of the “Is it Low T” movement has resulted in an increase of men >40 years old seeking testing for testosterone deficiency (TD) and treatment with testosterone replacement therapy (TRT). The FDA has mandated that TRT inserts should include warnings about a variety of possible risks such as venous thrombosis,prostate cancer, diabetes, and cardiovascular health risks. In response several societies have issued guidelines to address the use of TRT. The purpose of this review is to evaluate the variability in treatment and monitoring of TD and TRT. A literature search was performed to evaluate the most recent guidelines on TD. There were no available guidelines from Asian, African or South American specialty societies published English language literature. Guidelines from Canada, Europe, and the United States including the American Association of Clinical Endocrinologist (AACE) the American Urologic

Association(AUA), and the Endocrine Society are evaluated. Comparisons between guidelines are compiled in Tables and their level of evidence evaluated. All guidelines were in concurrence that a desire to maintain male fertility should be universally considered a contraindication to TRT. While other contraindications and risks associated with TRT such as cardiovascular disease or prostate cancer varied widely. Follow up assessment recommendations such as cardiac, bone density, and digital rectal exam also are non-congruent. The guidelines on TD reflect the lack of consensus between specialty societies, paucity of data, and need for further research on testosterone replacement treatment of TD.

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The direct to consumer marketing of the “Is it Low T” movement has resulted in an increase of men >40 years old seeking testing for testosterone deficiency (TD) and treatment with testosterone replacement therapy (TRT). The FDA has mandated that TRT inserts should include warnings about a variety of possible risks such as prostate cancer, diabetes, and cardiovascular risks. In response societies have issued guidelines to address the use of TRT. The purpose of this review is to evaluate the variability in treatment and monitoring of TD and TRT. A literature search was performed to evaluate the most recent guidelines on TD. Guidelines from Canada, Europe, and the U.S. including the American

Association of Clinical Endocrinologist (AACE), the American Urologic Association (AUA), and the Endocrine Society are evaluated. Comparisons are compiled in Tables and level of evidence evaluated. All guidelines were in concurrence that a desire to maintain male fertility is a contraindication to TRT. While other contraindications and risks of TRT such as cardiovascular disease or prostate cancer varied. Follow up assessment recommendations such as cardiac, bone density, and digital rectal exam are non-congruent. The guidelines on TD reflect the lack of consensus between specialty societies, paucity of data, and need for further research on TRT use in TD.

INTRODUCTION

The direct to consumer marketing of the “Is it Low T” movement has resulted in an increase of men over 40 years old seeking testing for testosterone deficiency (TD) and treatment with testosterone replacement therapy (TRT)[1, 2]. The uptrend caused the Food and Drug Administration (FDA) to warn against misleading marketing campaigns by drug companies and call for further research on TRT use in men with low testosterone of unknown etiology as well as treatment efficacy in elderly populations[2]. In addition, the FDA ruled that TRT inserts should include warnings about a variety of possible risks associated such as possible prostate cancer, venous thrombosis, diabetes, and cardiovascular health risks[3]. In response several governing bodies have issued guidelines to address the use of TRT in the setting of TD. However recommendations for treatment and follow up vary widely across specialties and countries. As a result of these contradictions have caused confusion among providers and can cause deviations from some basic treatment principles. Hence there is a need to provide the health care providers with a comprehensive document that will compare and contrast recommendations from the relevant specialty societies and the level of evidence these are based upon.

The purpose of this review is to evaluate the variability in treatment and monitoringof TD and TRT in guidelines from the world literature. There were no available guidelines from Asian, African or South American specialty societies published in English language literature. The recommendations from Canada[4], Europe[5], and the United States including the American Association of Clinical

Endocrinologist (AACE) [6] the American Urologic Association(AUA)[7-10], and the Endocrine Society[11] are included in this article. This review will highlight consensus opinions regarding the formulations of TRT, risks, contraindications and follow up to elucidate best practices.It will also identify discrepancies between guidelines from each association and between the two most recent TD guidelines from the AUA.

METHODS

A literature search was performed to evaluate the most recent guidelines on TD available in English literature. The search for the guidelines was performed October 22nd, 2018 via Pubmed, Uroweb, AUA, and AACE websites. There were no available guidelines from Asian, African or South American specialty societies in English language literature.Guidelines were included from the following four organizations:Canadian Men's Health Foundation Multidisciplinary Guidelines Task Force on Testosterone Deficiency (CMHF), European Association of Urology (EAU), and AUA, AACE, and the Endocrine Society.In addition, new guidelines by the AUA and the Endocrine Society were released and included for review on April 2nd, 2018. The literature was reviewed with an emphasis on the organizations' guidelines, position statements, white papers, and consensus statements. Emphasis was placed on comparing recommended work up prior to initiation of TRT, associated risks, contraindications, formulations of testosterone, and suggested follow-up for TRT. Guidelines were critically evaluated and compared with special attention to

variability and level of evidence on which these were based upon. (Appendix 1 and 2).

SOURCE OF PUBLISHED GUIDELINES

Description and comparison of levels of evidence and grade of recommendations can be found in Appendix 1 and Appendix 2.

EAU

The EAUMale Hypogonadism Panel worked to create the current recommendations. Recommendations by the panel were based on a systematic review of literature that includedarticles published before November 2014, the current recommendations were constructedusing 118 citations.The articles with the highest level of evidence were selected in accordance theOxford Centre for Evidence-Based Medicine Levels of Evidence[5].

CMHF

The CMHF Multidisciplinary Guidelines Task Force on TD commissioned 2 systematic reviews that were performed by a librarian and a pharmacist in December 2013 and updated in April 2014.The final guidelines were based off of 454 citations. The Task Force adopted consistent language to describe the level of evidence and strength of recommendations, as recommended by the GRADE Working Group[4, 12].

"OLD" AUA

The documents referred to as the "old" AUA guidelines throughout the review encompass now archived documents including: AUA Position Statement on Testosterone Therapy most recently revised in 2015[9], AUA White Paper on

Laboratory Diagnosis of TD 2013[7], and AUA consensus statement on Testosterone Testing published in 2010[8]. The aforementioned documents were the only documents available on the AUA website when performing a search for testosterone deficiency guidelines in October of 2017.

2018 AUA

The AUA appointed a panel to construct the newest guidelines published in 2018. The authors utilized a systematic review that encompassed articles published between January 1, 1980- February 6, 2017, 546 references were used to support guidelines statements. Levels of evidence and strength of recommendations utilized AUA nomenclature, linking statement type to evidence of strength[10].

AACE

The AACE Hypogonadism Task Force constructed the guidelines for clinical practice for adult men with hypogonadism published in 2002. Guidelines were constructed based off of literature reviews, with the use of 77 citations. Grades and level of evidence were not presented in the guidelines[6].

ENDOCRINE SOCIETY

The Endocrine Society guidelines were based on the best available evidence found in two systematic reviews, other reviews, and individual studies. The guidelines have 156 citations total and were developed using the Grading of Recommendations,Assessment, Development, and Evaluation approach to describe the strength of recommendations and the quality of evidence. The

guidelines published in 2018 were to serve as an update to the “Testosterone Therapy in Men With Androgen Deficiency Syndromes”published in 2010[11].

Comparison

Based on the above sources the new 2018 AUA guidelines included the most citations with 546 supporting sources. While 77 articles served as sources of information for the AACE guidelines.

DISCUSSION

Guidelines are in consensus that improvement of signs and symptoms should be a main goal of treatment. All guidelines suggest adjustment of therapy be individualized to the patient. In patients with inadequate response to treatment clinicians should change the form of delivery, dose, or frequency of administration. Suggested and prohibited preparations, indications, and contraindications of TRT between guidelines differ.

Goal of testosterone therapy

The Endocrine Society, EAU, and old AUA guidelines cited no reference ranges for testosterone therapy treatment goal. A total testosterone level between 450-600ng/dLis recommended by the 2018 AUA (Conditional Recommendation; Grade C)[10, 13]. In contrast the AACE recommends a physiologic range of serum testosterone levels between 280 and 800 ng/dL[6].The CMHFsuggests treatment be aimed at maintaining a mid-normal range for healthy young men which they cite as 404–505 ng/dL[14].

Preparations of testosterone

All organizations provide descriptions with advantages and disadvantages of available preparations of testosterone therapy except for the old AUA guidelines. The 2018 AUArecommends against prescribing alkylated oral testosterone (Moderate recommendation; Grade B)[10]. AACE takes a similar stance and recommends against the use of oral agents due to adverse lipid and hepatic changes, in addition to poor androgenic effects[15]. However, the Endocrine Society[11],CMHF[4], and EAU[5] do not recommend against the use of oral undecanoate.

EAU[5] recommends short acting preparations when initiating treatment, thisdiffers from the majority of the other societies. EAU notes that short acting preparations can be halted in case of adverse side effects (B; 3)[16].

Discussion of transference risk in men using testosterone gels and creams is strongly recommended by the 2018 AUA (Strong recommendation; Grade A) due to case reports citing adverse effects on women and children including virilization and precocious puberty respectively[17-21]. They also recommendcommercially manufactured testosterone productsover compounded testosterone(Conditional recommendation; Grade C)[10, 22] because compounded testosterone is not regulated by the FDA and can vary in potency[10]. CMHF note that published data is lacking on the subject of compounded testosterones safety and efficacy[4].

Alternative Therapies

The 2018 AUA guidelines supports the use of alternative therapies in men with TD desiring to maintain fertility (Conditional Recommendation; Evidence

Level: Grade C)[10]. Recommended therapies include aromatase inhibitors, anastrazole, human chorionic gonadotropin (hCG), selective estrogen receptor modulators (SERM), or a combination. The mechanisms of action, as well as advantages and disadvantages of each therapy are presented in the guidelines[10].

The EAUrecommends hCGuse but limits it to patients with hypogonadotropic hypogonadism undergoing fertility treatment (B; 1b)due to insufficiency of information regarding long-term use[5]. The Endocrine Society cites that clomiphene citrate, a SERM, has demonstrated neither efficacy nor safety in RCTs, although it has empirically been used in men with hypogonadotopic hypogonadism(1, +++) [11]. The AACEpresents information on alternative therapies however makes no specific recommendations[6]. Ultimately, all guidelines acknowledge that choice of preparation of testosterone therapy or pursuit of alternative treatment should be a discussion held between the patient and the physician.[4-6, 9-11].

Indications and contraindications for testosterone therapy

All guidelines agree that testosterone therapy is indicated in in the presence of clinical and historical findings of TD[4-6, 9-11]. However, guidelines reviewed differ in the contraindications to receiving testosterone therapy (Table 1). All guidelines note that shared decision-making should be used when prescribing TRT. It is emphasized that patients should be presented with the risks, benefits, indications, and contraindications when deciding if the therapy is right for them[4-6, 9-11]. The EAUand 2018 AUA guidelines specify that men

should only be considered for TRT if weight loss, lifestyle modification, and good treatment of comorbidities has proven unsuccessful (EAU: A; 2, AUA: Conditional recommendation; Grade B)[5, 10].

Fertility

Maintenance of fertility and patients with infertility that desire fertility are contraindicationsto TRT across all guidelines (EAU: A; 1b, CMHF: Strong recommendation; High-quality evidence, 2018 AUA: Strong recommendation; Grade B, Endocrine Society: 1; ++, AACE: n/a, older AUA: n/a)[4-6, 9-11]. Each organization presents similar evidence regarding TRT on the suppression of spermatogenesis[23-27].

Neoplasms

All guidelines except those from the AUA state that a history of breast cancer is a contraindication to TRT (CMHF: Weak recommendation; Moderate evidence, Endocrine Society: 1; ++, AACE: n/a, EAU: n/a)[4-6, 9-11].Guidelines cite that strong evidence is lacking about theassociation between TRT and development of breast cancer, although male breast cancer has been reported albeit on a small numbers of patients[5, 6, 28-30].

Men who desire testosterone therapy with historical, treated, and active prostate cancer remains an area that requires further research. Each guideline has specific recommendations on the topic but no clear consensus exists.

The 2018 AUA guidelines recommend that men status post radical prostatectomy with favorable margins and undetectable PSA can be considered for testosterone therapy (Expert Opinion)[10]. This recommendation is supported

by the lack of evidence supporting biochemical recurrenceassociated with testosterone therapy in this specific population,with the exception of one study conducted by Pastuszak et al., (2013)[31-34]. The EAU and CMHF takes a similar stance, men who have undergone surgery for prostate cancer can be eligible for TRT, EAU specifies eligibility depends on recurrence risk (EAU: B; 3, CMHF: Weak recommendation; Low-quality evidence)[4, 5].

According to the 2018 AUA and CMHF men who have undergone radiation therapy for prostate cancershould be eligible for treatment, but only after an elapse of time to allow for possible gain of function (2018 AUA: Expert Opinion, CMHF: Weak recommendation; Low-quality evidence)[4, 10]. In contrast, the Endocrine Society was unable to make a recommendation regarding TRT in men with a history of prostate cancer however, they notethat men with an unevaluated prostate nodule or induration, and men with a PSA> 4ng/ml or >3ng/ml in high risk populations should not receive testosterone treatment (1; ++)[11].

The CMHF, EAU, and Endocrine Society recommends that in the presence of active or metastatic disease TRT is contraindicated (CMHF: Strong recommendation; Moderate to high-quality evidence, EAU: B; 3, Endocrine Society: 1; ++)[4, 5, 11]. While the older AUA guidelines do not comment on this populations eligibility, the 2018 AUA leaves the decision up to the patient and the provider after benefits and risks are discussed due to the lack of definitive evidence demonstrating that testosterone therapy is not safe in active or metastatic prostate cancer patients (Expert Opinion)[10].

Sleep Apnea

The EAU concludes that there is no consistent evidence correlating TRT with obstructive sleep apnea (OSA) and state no evidence has supported that TRT can result in the onset or worsening of the condition[5]. In contrast, the Endocrine Society and AACE recommend against the use of testosterone treatment in patients that suffer from severe sleep apnea (Endocrine Society: 1; ++, AACE: n/a) [6, 11, 35].

Benign Prostatic Hypertrophy (BPH)

Both AUA guidelines do not comment on the BPH populations eligibility for testosterone therapy, while the AACE and CMHF state men with BPH and TD are eligible for therapy and note that urinary or prostate symptoms should be followed closely (AACE: n/a, CMHF:Weak recommendation; Very low quality evidence)[4, 6]. Contrarily, the Endocrine Society and the EAUrecommends against the use of testosterone therapy in men with severe lower urinary tract symptoms due to BPH (Endocrine Society: 1; ++, EAU: n/a)[5, 11]. Men with severe lower urinary tract symptoms at baseline have been excluded from testosterone therapy trials therefore safety of testosterone treatment has not been measured in this population [36, 37].

Cardiovascular disease

The 2018 AUA and Endocrine Society cite evidence is lacking on cardiovascular disease and TRT but make recommendations that testosterone should not be initiated in men with a history of cardiovascular events for a period of three to six months, and six months respectively after the event (2018 AUA:

Expert Opinion, Endocrine Society: 1;++)[10, 11].The CMHF and EAU suggest therapy be restricted to men with stable cardiovascular disease only after a discussion of the potential risks and benefits in combination with careful clinical monitoring (CMHF: Weak recommendation; Low quality evidence, EAU:A; 1b)[4, 5]. The EAU adds that men with chronic cardiac failure in need of TRT can be considered (A; 1b)[5]. All societies acknowledge that FDA warnings about cardiovascular events on testosterone products exist, however they note lack of adequately powered RCTsto draw meaningful data from the population.

Diabetes Mellitus Type 2 (DM2)

While there is agreement among societies that insulin resistance can be a sign of TD, and a higher prevalence of TD exists in the DM2 population, the treatment of men with DM2 and TD is controversial[38-43]. The diagnosis of DM2 is considered and indication for testosterone treatment by the EAU (B; 2)[5]. They support this recommendation stating that TRT has shown positive effects in hypogonadal men with impaired glucose tolerance, specifically aiding glycemic and lipid control, insulin resistance, adiposity and decreasing mortality[5, 44, 45].

The 2018 AUA neither recommend nor discourages DM2 patients with TD from getting treatment due to conflicting data (Moderate recommendation; Grade B)[10]. The CMHF and Endocrine Society do not indicate treatment in this population to avoid burden of monitoring and unknown long-term risks (CMHF: n/a, Endocrine Society: 1; ++)..

HIV

HIV infected men, even those being treated with antiretroviral therapy,

have a high prevalence of TD[35, 46-52]. In men with HIV, low testosterone, and weight loss (for which other causes of loss have been excluded), the Endocrine Society recommends short-term testosterone therapy, no longer than 6 months, to induce and maintain body weight and lean mass gain (2, ++)[11]. Similarly, the CMHF, EAU, and 2018 AUA guidelines note that this population of men is eligible for TRT (CMHF: Weak recommendation; Low quality evidence, EAU: B; 2, 2018 AUA: Moderate Recommendation; Grade B)[4, 5, 10].

Thrombophilia

The EAU recommends that men withvenous thromboembolism (VTE) should be treated with caution and careful clinical monitoring (A; 1b) due to a study that showed VTE association with TRT[5, 53]. The Endocrine Society recommends against the use of TRT in men with VTE or thrombophilias (1, ++) [11]. However, the2018 AUA guidelines do not preclude the population from receiving therapy[9, 10]. All societies note that there is a lack of RCTs on VTE to draw meaningful inferences[4-6, 9-11].

Miscellaneous

The CMHF is the only guideline to recommend a 3 month trial treatment with testosterone in men with a clinical picture strongly suggestive of TD but testosterone levels in the low-normal range (Weak recommendation; Very-low-quality evidence)[4]. They base this recommendation on a study conducted by Black et al. 2004 that suggests lack of accurate diagnosis of symptomatic late onset hypogonadism, and a trial therapy of testosterone for three months circumvents placebo effect and has minimal risks for adverse effects[54].

The Endocrine Society is the only organization to make age based recommendations on who should be eligible for treatment with testosterone. They recommend that risks and benefits be explained, possible monitoring of patients prostate, and shared decision making occur prior to therapy in hypogonadal men above the age of 40 at an increased risk of prostate cancer (African American or patients with first degree relatives with prostate cancer) and men 55 to 69 with a life expectancy >10 years (2; +)[11]. Additionally they recommend against the routine prescribing of testosterone therapy to men who are greater than 65 with low testosterone concentrations (1; ++), they suggest only those with unequivocally low testosterone be considered after a risk benefit discussion is conducted (2; ++)[11].

Work up required before testosterone therapy

Comparison of baseline tests and exams recommended by reviewed guidelines is presented in Table 2. All guidelines recommended testosterone as a baseline lab[4-6, 9-11].

Hemoglobin and hematocrit

Polycythemia is the most common adverse effect associated with TRT, therefore prior to offering testosterone therapy, all guidelines except the older AUA recommend clinicians measure hemoglobin and hematocrit and inform patients regarding the increased risk of polycythemia (2018 AUA: Strong Recommendation; Grade A, AACE: n/a, EAU: 3;A, CMHF: Strong recommendation; High quality evidence, Endocrine Society: 1, ++)[4-6, 10, 11]. Specifically, the 2018 AUA guidelines and AACEstate men who have

hematocrits>50% treatment should be withheld, while the EAU uses >54% as the cut off [6, 10].

Estradiol and breast assessment

The 2018 AUA guidelines are the only to recommendserum estradiol measurement in TD patients who present with breast symptoms or gynecomastia prior to the commencement of TRT (Expert Opinion)due to the conversion of testosterone to estradiol[10]. The 2018 AUA, EAU, and AACE, recommend breast assessment prior to beginning treatment due to concerns for breast cancer and symptomatic gynecomastia development(2018 AUA: Expert Opinion, EAU: A; 1a, AACE: n/a)[5, 10, 11].

PSA and Digital rectal exam (DRE)

TheEAU, AACE,Endocrine Society, and theCMHF recommend a PSA and DRE at baseline but do not limit it to any age group (EAU: C; 4, AACE: n/a, Endocrine Society: n/a,CMHF: Weak recommendation; Low quality evidence (PSA), Weak recommendation; Very low quality evidence (DRE))[4-6, 11].While the 2018 AUA limits pre-treatment measurement of PSA to only men over 40 years of age (Clinical Principal)[10].

Cardiovascular exam

Cardiovascular risk factor assessment and treatment of modifiable cardiac risk factors in those with pre-existing cardiovascular disease prior to therapy is recommended by the EAU and the 2018 AUA (EAU: A; 1a, 2018 AUA:Strong recommendation; Grade B)[5, 10].The Endocrine Society recommends risk factor assessment and adds screening for the following: uncontrolled or poorly

controlled heart failure, myocardial infarction or stroke within the last six months (1, ++)[11]. The society does note testosterones potential to affect lipid profiles however, does not recommend baseline testing of lipids[55, 56]. The AACE is the only group to recommend an initial lipid profile due to the un-aromatized anabolic steroid used in certain testosterone preparations that have the ability to increase LDL and lower HDLs[6].

Reproductive Health Evaluation

The 2018 AUA guidelinesacknowledge testosteroneseffect on fertility and advise that men with TD who are interested in fertility should have a reproductive health evaluation performed prior to treatment (Moderate Recommendation; Grade B)[10]. Other organizations lack recommendations of reproductive health evaluations prior to initiating TRT.

Risksassociated with TRT

Each guideline recommends discussion of risks associated with treatment before initiation of therapy.Comparison of testosterone treatment risks across guidelines is presented in Table 3. There is consensus between all guidelines that infertility is a risk factor and that prostate cancer development and cardiovascular events as a result of TRT has inconclusive evidentiary support.

Prostate risk

Association of prostate cancer risk and TRT is an area that all guidelines agree is area that needs further elucidation. All organizations except the EAU cite that evidence at the time of publication was inconclusive regarding the risks of testosterone therapy on prostate cancer[4-6, 9, 11]. The 2018 AUA supports this

assertion with a formal recommendation to inform patients of the lack of evidence linking testosterone therapy to the development of prostate cancer (Strong recommendation; Grade B)[10].

The Endocrine Society recommends clinicians speak with patients about risk and benefits of evaluation of prostate cancer and prostate monitoring (2, +), however they cite that the relationship between testosterone administration and prostate cancer is still poorly understood [11].

Sleep apnea risk

As discussed previously in the *Eligible populations* section of the review the EAU notes that there is no association between the development of sleep apnea with TRT. In contrast, the AACE and the Endocrine Society note the development of OSA can be associated with testosterone therapy[6, 11].

Cardiovascular risk

All guidelines acknowledge that further evidence and more conclusive data from higher quality studies is called for to create formal recommendations on cardiovascular risk associated with TRT (EAU: 1a,CMHF: n/a, Endocrine Society: n/a, AACE: n/a, Old AUA: n/a)[4-6, 9, 11]. The 2018 AUA is the only group to recommend that prior to treatment clinicians should counsel patients that it cannot be definitively stated whether TRT increases or decreases the risk of cardiovascular events (Moderate Recommendation; Grade B)[10].

Erythrocytosis/Thromboembolism/Polycythemia risk

The Endocrine Society notes that TRT was found to be associated with

higher rates of erythrocytosis in a commissioned systematic review[57], and some studies have reported higher frequency in older men versus younger men[55].In those that develop erythrocytosis the society recommends phlebotomy[11]. The EAU, AACE, old AUA guidelines and CMHFdo not comment on erythrocytosis but do note that testosterone can increase hematocrit and has been associated with hyperviscosity and thrombosis[4-6, 53, 58, 59].

In regards to thromboembolism the Endocrine Society, EAU, CMHF, and 2018 AUA note that there are too few studies associating VTE with TRT[4, 5, 10, 11, 60, 61]. The 2018 AUA recommends patients should be informed that no conclusive evidence exists linking testosterone therapy to higher incidence of VTE (Moderate recommendation; Grade C)[10].

Follow up and monitoring of testosterone therapy

Follow up of TRT is recommended by all guidelines reviewed, although time intervals, tests, and exams recommended vary. Recommended follow up has been organized in Table 4.

General timing of follow up

All guidelines recommend general assessment of response and for adverse effects but specific follow up times vary(CMHF: Strong recommendation; High quality evidence, EAU: C;4, AACE: n/a, Endocrine Society:Ungraded Good Practice Statement, 2018 AUA: n/a)[4-6, 11].

Testosterone levels

CMHF and Endocrine Societyrecommend testosterone levels be followed every 3 and 6 months after onset of therapy and then annually thereafter if stable

(CMHF: Weak recommendation; Low-quality evidence, Endocrine Society: Ungraded Good Practice Statement)[4, 11].The 2018 AUA recommends that men get testosterone levels checked every 6 months while on treatment and provide ideal follow up intervals according to formulations of testosterone used (Expert Opinion)[10]. The EAU, AACE, and the Endocrine Society also provide ideal follow up intervals according to the formulations of testosterone available(EAU: n/a, AACE: n/a, Endocrine Society: Ungraded Good Practice Statement)[6, 10, 11].

Hematocrit and Hemoglobin levels

Clinicians should note that erythropoiesis can become evident at 3 months and peaks around 12 months of TRT[62]. The EAU and Endocrine Societyrecommend follow upof hematocrit and hemoglobin at 3 and 6 months after onset of therapy and should be monitored annually there after (EAU: C; 4, Endocrine Society: Ungraded Good Practice Statement)[5, 11]. The CMHF only recommends hematocrit, as it is more predictive of risk of thrombosis than hemoglobin levels but recommends the same time interval as the EAU and Endocrine Society (CMHF: Strong recommendation; High quality evidence, [4, 35, 63]. The AACE differs as it recommends hematocrit be determined every 6 months for the first 18 months and then annually thereafter if stable.The 2018 AUA guidelines specify that during TRT titration clinical judgment should be exercised to decide the need for hemoglobin and hematocrit monitoring while in the stable phase they recommends levels every 6-12 months or sooner(Expert Opinion)[10]. The old AUA guidelines comments that hematocrit be apart of

follow up do not mention time of follow up[9].

PSA

The CMHF and EAUrecommends a follow up of PSA at 3 and 6 months and then annually (CMHF: strong recommendation; moderate to low quality evidence, EAU: C; 4)[4, 5]. The Endocrine Society differs citing that PSA be followed in those that choose prostate monitoring every 3 to 12 months and after a year of therapy monitoring should conform to standard screening guidelines based on the patients race and age (Ungraded Good PracticeStatement)[11].

While the old AUA guidelines suggest that PSA be apart of therapy monitoringno specific follow up schedule is recommended[9]. The 2018 AUA guidelines recommend clinicians utilize a shared decision making approach in accordance with the AUA Early Detection of Prostate Cancer Guidelinein men without a history of prostate cancer clinicians (Expert Opinion)[10, 64]. The Panel also recommends that prostate cancer patients on TRT should have their PSA levels monitored on the same schedule as men without TD, but clinicians may chose to increase frequency of testing (Expert Opinion)[10].

DRE

The Endocrine Society recommendsDRE be included in prostate monitoring for those who chose (Ungraded Good PracticeStatement). However, TRT has been shown to increase prostate volume over the first year of treatment thusDRE is recommended by the CMHF and AACE to be performed at 6 months, then annually following onset of treatment (CMHF: Weak recommendation; Very-low-quality evidence, AACE: n/a)[4, 6, 62, 65].The AACE is the only society to

add that a prostate related symptoms assessment should be administered at same intervals of prostate exams [6].

Cardiovascular

The EAU recommends close clinical assessment of cardiovascular diseasewhile a patient is on TRT (A; 1b)[5]. Lipid panel in follow up is only recommended by the AACE, they specify it should be followed every 6-12 months of therapy and then yearly thereafter, due to non-aromatized nature of testosterone used in preparations that can increase LDL and lower HDL levels(AACE: n/a)[6].

Bone mineral density (BMD)

The EAU does not make a formal recommendation onBMD but does state that it should only be monitored in men who had abnormal density before initiation of therapy[5]. Similarly the Endocrine Society recommend BMD be followed in men with osteoporosis on testosterone therapy at an interval of 1 to 2 years to determine whether it is being appropriately maintained or if the patient requires additional therapy (Endocrine Society: 2;++)[11]. While the AACE notes that BMD should be done in men with TD regardless if they are receiving therapy to aid in decision making about treatment options(AACE: n/a)[6]. The 2018 AUA and Endocrine Society acknowledge that BMD could be improved with testosterone therapy however evidence is inconclusive (2018 AUA: Moderate Recommendation; Grade B, Endocrine Society: n/a)[10, 11].

Sleep apnea

The AACE recommends follow up of sleep apnea in men receiving TRT by

asking about daytime fatigue as well as disordered sleep (AACE: n/a)[6].

Others

The 2018 AUA recommends that during the titration phase of testosterone therapy it is optional to test estradiol. Additionally, they recommend in the stable phase of testosterone treatment patients who develop breast symptoms or gynecomastia, patients on androgen inhibitors, and those on SERMs should get an estradiol level checked (Expert Opinion)[10]. In men with TD started on SERM treatment they recommend a LH level about 4 weeks after initiation, they go on to recommend an LH level in patients who stop responding to therapy(Expert Opinion)[10].

In regards to men being treated with medication for hyperprolactinemia the 2018 AUA recommends a prolactin level every 6-12 months (Expert Opinion)[10]. For men undergoing alternative therapies such as anastrozole, hCG, and clomiphene citrate follow up labs needto be collected at least 4 weeks after initiation (Expert Opinion)[10].

Cessation of Treatment

The old AUA guidelines provide no clear time line or criteria for cessation of testosterone treatment. In patients who experience normalization of total testosterone but fail to achieve symptom improvement after 3-6 months of treatment the 2018 AUA recommends discussion of cessation of testosterone therapy (Clinical Principle)[10]. They suggestother etiology of symptoms should be further explored in this population. The Panel does explain two exceptions to this, the first being men with unexplained anemia that improves with testosterone

therapy, a continuation can be considered in the absence of other symptom improvement. The second exception is if patients do not have symptoms but have documented BMD loss[10]. The CMHF recommends that therapy be discontinued if there is no improvement after an adequate therapeutic trial (Weak recommendation; Moderate quality evidence) [4]. TheEndocrine Society, EAU, and the AACE do not have specific recommendations on cessation however they do recommend cessation if contraindications arise throughout their guidelines and recommendations, for example an elevated hematocrit[5, 6, 11].

CONCLUSION

TRT is a proven approach for the management of TD and all guidelines agree that historical symptoms and clinical lab findings indicative of low testosterone are indications for treatment. While all societies agree that desire to maintain fertility, polycythemia, and active prostate cancer are contraindications other contraindications vary between guidelines. Little consensus exists regarding patients with history of prostate cancer, sleep apnea, VTE/thrombophilia,or diabetes being eligible for treatment.

Recommendations for baseline and follow up labs have improved in the 2018 AUA guidelines from the older version with specific tests and their designated time intervals being recommended. All current guidelines agree with the use of testosterone and hematocrit labs at baseline and in follow up. Estradiol measurement at baseline and reproductive health evaluation was only recommended by the 2018 AUA, while lipid profile was only recommended by the AACE. All guidelines also recommend use of PSA testing at baseline and follow

up, with 2018 AUA and Endocrine Society making age specific recommendations. The only society to recommend lipid profile and prostate related symptoms assessment in follow up is the AACE. Follow up DRE exams were recommended by all guidelines except the AUA. The EAU, AACE, and Endocrine Society were the only to recommend BMD monitoring in those with pre-existing osteoporosis.

All guidelines agree that infertility is a risk of testosterone treatment. The EAU does not associate testosterone treatment with the risk of developing sleep apnea, while the Endocrine Society and AACE cite it as a risk. All guidelines agree that evidence is inconclusive in regards to the risk of prostate cancer or cardiovascular disease with the use of TRT.

Overall, the guidelines reviewed showcased the wide variations that exist on the topic of TRT contraindications, risks, baseline and follow up labs and exams. Until topics are further clarified it is unlikely that there will be consensus between societies, more research is called for on the subject of TRT. Thus, it remains vital that individual clinicians utilize shared decision making and discuss the appropriate risks and benefits with patients in order to come to a solution that represents the best fit for each scenario.

Table 1. CONTRAINDICATIONS: Analysis and comparison of testosterone therapy or testosterone replacement therapy contraindications recommended by guidelines from Canada, Europe, and America.

		Canada	Europe	United States			
				Old AUA	2018 AUA	Endocrine Society	AACE
Populations eligible for testosterone therapy	Infertility	CI	CI	CI	CI	CI	CI
	Active PCa	CI	CI	Inc Evidence	Relative CI	CI	CI
	Hx of PCa	Relative CI	Relative CI depends on recurrence risk	Inc Evidence	Not CI	Inc Evidence	n/a
	Treated PCa	CI	Relative CI depends on recurrence risk	Inc Evidence	Not CI	Inc Evidence	n/a
	Breast Ca	CI	CI	n/a	n/a	CI	CI
	Sleep Apnea	n/a	Not CI	n/a	n/a	CI	Relative CI
	LUTS/BPH	Relative CI	CI	n/a	n/a	CI	Not CI
	Cardiovascular Disease	Relative CI	Relative CI	Inc Evidence	CI, only eligible 3-6 months post event	CI if uncontrolled HF, MI or stroke within 6 months	Inc Evidence
	Type 2 Diabetes	CI	Not CI	n/a	Inc Evidence	CI	n/a
	HIV	Not CI	Not CI	n/a	Not CI	Not CI	n/a
	Thrombophilia or VTE	Inc Evidence	Relative CI	n/a	Not CI	CI	n/a
	Polycythemia	CI, if Hct>54%	CI, if Hct>54%	n/a	CI, if Hct>50%	CI, if elevated Hct	Relative CI

Key:
PCa- Prostate cancer Hx- history LUTS- lower urinary tract symptoms n/a- not mentioned
BPH-benign prostatic hypertension Mets- metastatic Relative CI- relative contraindication
Inc Evidence- inconclusive evidence HF- heart failure MI: myocardial infarction
Hct- hematocrit CI- contraindication

Table 2. BASE LINE LABS AND ASSESSMENTS: Comparison of baseline tests and exams recommended by Canada, Europe, and America.

		Canada	Europe	United States			
				Old AUA	2018 AUA	Endocrine Society	AACE
Baseline Labs	Testosterone	x	x	x	x	x	x
	Hct	x	x	n/a	x	x	n/a
	Hb	n/a	x	n/a	x	n/a	n/a
	Estradiol	n/a	n/a	n/a	x	n/a	n/a
	PSA	x	x	n/a	x *	x *	x
	Lipid Profile	n/a	n/a	n/a	n/a	n/a	x
Baseline Exams and Assessments	DRE	x	x	n/a	x *	x *	x
	Cardiac	n/a	Yes, RF assessment if pre-existing disease	n/a	Yes, RF assessment if pre-existing disease	Yes, RF assessment if pre-existing disease	n/a
	Breast	n/a	x	n/a	x	n/a	x
	Reproductive health evaluation	n/a	n/a	n/a	x-if interested in fertility	n/a	n/a

Key:
x- indicated in recommendations n/a- not mentioned in recommendations
* age specific recommendation Hct- hematocrit Hb- hemoglobin
PSA-prostate specific antigen DRE- digital rectal exam
RF-risk factors TD- testosterone deficiency

Table 3. RISKS: Comparison of risks associated with testosterone therapy in guidelines by Canada, Europe and America.

		Canada	Europe	United States			
				Old AUA	New AUA	Endocrine Society	AACE
Risks associated with TRT	Infertility	Yes	Yes	Yes	Yes	Yes	Yes
	Prostate Ca	Inc Evidence	Inc Evidence	Inc Evidence	Inc Evidence	Inc Evidence	Inc Evidence
	Sleep apnea	n/a	No	Inc Evidence	n/a	Yes	Yes
	CVD	Inc Evidence	Inc Evidence	Inc Evidence	Inc Evidence	Inc Evidence	Inc Evidence
	VTE	Relative	Inc Evidence	n/a	Inc Evidence	Inc Evidence	n/a

Key:
n/a- not mentioned in recommendations Ca- cancer CVD- cardiovascular disease
VTE- venous thromboembolism

Table 4. FOLLOW UP LABS: Comparison follow up labs and assessments recommended by Canada, Europe, and America.

		Canada	Europe	United States			
				Old AUA	2018 AUA	Endocrine Society	AACE
Follow up Labs	Testosterone	x	x	x	x	x	x
	Hct	x	x	x	x	x	x
	Hb	n/a	x	n/a	x	n/a	n/a
	PSA	x	x	x	x *	x *	x
	Lipid Profile	n/a	n/a	n/a	n/a	n/a	x
Follow up Exams and Assessments	DRE	x	x	n/a	n/a	x *	x
	Prostate related symptom assessment	n/a	n/a	n/a	n/a	n/a	x
	Cardiac	n/a	Yes, if pre-existing disease	n/a	n/a	n/a	Yes, lipids
	Bone Density	n/a	x- if abnormal before therapy	n/a	n/a	x	x
	Sleep Apnea	n/a	n/a	n/a	n/a	n/a	x

Key:
x- indicated in recommendations n/a- not mentioned in recommendations
* age specific recommendation Hct- hematocrit Hb- hemoglobin
PSA-prostate specific antigen DRE- digital rectal exam
RF-risk factors TD- testosterone deficiency

Appendix 1. Level of Evidence Definitions (adapted from AUA, CMHF, EAU, and AACE)

AUA	2018 AUA	CMHF	EAU	AACE	Endocrine Society
N/A	A: High certainty Benefit>Risk/burden or vice versa Net benefit or harm is substantial Applies to most patients andin most circumstances and future research is unlikely to change confidence	High Quality: Consistent evidence from RCTs or strong evidence from unbiased observational studies	1a: Evidence obtained from meta-analysis of randomized trials Ib: Evidence obtained from at least one randomised trial.	N/A	++++: High quality Consistent evidence from RCTs or strong evidence from unbiased observational studies
N/A	B: Moderate certainty Benefit>Risk/burden or vice versa Net benefit or harm is substantial Applies to most patients andin most circumstances but better evidence could change confidence	Moderate Quality: Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence) or unusually strong evidence from unbiased observational studies	2a: Evidence obtained from one well-designed controlled study without randomization 2b: Evidence obtained from at least one other type of well-designed quasi-N/A experimental study	N/A	+++: Moderate quality of evidence Evidence from RCTs with important limitations (inconsistent results, methodological flaws, indirect or imprecise evidence) or unusually strong evidence from unbiased observational studies
N/A	C: Low certainty Benefit>Risk/burden or vice versa Net benefit or harm appears substantial Applies to most patients andin most circumstances but better evidence is likely to change confidence	Low Quality: Evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence	3: Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports 4. Evidence obtained from expert committee	N/A	++: Low quality of evidence Evidence for at least one critical outcome from observational studies, from RCTs with serious flaws, or indirect evidence

			reports or opinions or clinical experience of respected authorities		
N/A	N/A	Very Low Quality: Evidence for at least one of the critical outcomes from unsystematic clinical observations or very indirect evidence	N/A	N/A	+: Very low quality evidence Evidence for at least one of the critical outcomes from unsystematic clinical observations or very indirect evidence

Appendix 2. Grade Definitions (adapted from AUA, CMHF, EAU, and AACE) *note2018 AUA guidelines do not mention “grade” but do have nomenclature modifying statement type to evidence of strength which was adapted for this table

AUA	2018 AUA	CMHF	EAU	AACE	Endocrine Society
N/A	Strong recommendation: Net benefit or harm substantial	Strong recommendation: based on the quality of the supporting evidence, the level of uncertainty between desirable and undesirable clinical effects or diagnostic reliability, and therapeutic preferences.	A: Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial.	N/A	1: Strong recommendation Used to modify LOE Benefit clearly greater than harms/burden or vice versa
N/A	Moderate Recommendation: Net benefit or harm moderate	N/A	B: Based on well-conducted clinical studies, but without randomized clinical trials	N/A	N/A
N/A	Conditional Recommendation: No apparent net benefit or harm	Weak Recommendation: based on the quality of the supporting evidence, the level of uncertainty between desirable and undesirable clinical effects or diagnostic reliability, and therapeutic preferences.	C: Made despite absence of directly applicable clinical studies of good quality	N/A	2: Conditional recommendation Used to modify LOE Benefit closely balanced with harms/burden Requires more carefulconsideration of the circumstances, values, and preferences to determine the best course of action
N/A	Clinical Principal: Component of clinical care that is widely agreed upon by clinicians for which there may or may not	N/A	N/A	N/A	N/A

	be evidence in the medical literature				
N/A	Expert Opinion: achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence	N/A	N/A	N/A	Ungraded Good Practice Statement: Direct evidence for thesestatements was either unavailable or not systematically appraised. Intention is to draw attentionand remind providers of these principles

References

1. Baillargeon, J., et al., *Trends in androgen prescribing in the United States, 2001 to 2011.* JAMA Intern Med, 2013. **173**(15): p. 1465-6.
2. Metzger, S.O. and A.L. Burnett, *Impact of recent FDA ruling on testosterone replacement therapy (TRT).* Translational Andrology and Urology, 2016. **5**(6): p. 921-926.
3. Administration, U.S.F.a.D. *FDA approves new changes to testosterone labeling regarding the risks associated with abuse and dependence of testosterone and other anabolic androgenic steroids (AAS)*. 2016; Available from: https://www.fda.gov/Drugs/DrugSafety/ucm526206.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery.
4. Morales, A., et al., *Diagnosis and management of testosterone deficiency syndrome in men: clinical practice guideline.* CMAJ : Canadian Medical Association Journal, 2015. **187**(18): p. 1369-1377.
5. G.R. Dohle (Chair), S.A., C. Bettocchi, and S.K. T.H. Jones, M. Punab, *Guidelines on Male Hypogonadism*, in *European Association of Urology*. 2015. p. 24.
6. Petak, S.M., et al., *American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients--2002 update.* Endocrine Practice: Official Journal Of The American College Of Endocrinology And The American Association Of Clinical Endocrinologists, 2002. **8**(6): p. 440-456.
7. Paduch, D.A., et al., *The laboratory diagnosis of testosterone deficiency.* Urology, 2014. **83**(5): p. 980-8.

8. Rosner, W. and H. Vesper, *Toward excellence in testosterone testing: a consensus statement.* J Clin Endocrinol Metab, 2010. **95**(10): p. 4542-8.
9. Directors, A.U.A.B.o., *AUA Position Statement on Testosterone Therapy.* 2014.
10. Mulhall JP, T.L., Brannigan RE, Kurtz EG, Redmon JB., Chiles KA, Lightner DJ, Miner MM, Murad MH, Nelson CJ, Platz EA, Ramanathan LA, Lewis RW *Evaluation and Management of Testosterone Deficiency: AUA Guideline.* J. Urol, 2018.
11. Bhasin, S., et al., *Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline.* J Clin Endocrinol Metab, 2018.
12. Guyatt, G.H., et al., *Guideline panels should not GRADE good practice statements.* J Clin Epidemiol, 2015. **68**(5): p. 597-600.
13. Khera, M., et al., *Adult-Onset Hypogonadism.* Mayo Clin Proc, 2016. **91**(7): p. 908-26.
14. Corona, G., G. Rastrelli, and M. Maggi, *Diagnosis and treatment of late-onset hypogonadism: systematic review and meta-analysis of TRT outcomes.* Best Pract Res Clin Endocrinol Metab, 2013. **27**(4): p. 557-79.
15. Bagatell, C.J. and W.J. Bremner, *Androgens in men--uses and abuses.* N Engl J Med, 1996. **334**(11): p. 707-14.
16. Parsons, J.K., et al., *Serum testosterone and the risk of prostate cancer: potential implications for testosterone therapy.* Cancer Epidemiol Biomarkers Prev, 2005. **14**(9): p. 2257-60.
17. de Ronde, W., *Hyperandrogenism after transfer of topical testosterone gel: case report and review of published and unpublished studies.* Hum Reprod, 2009. **24**(2): p. 425-8.
18. Merhi, Z.O. and N. Santoro, *Postmenopausal virilization after spousal use of topical androgens.* Fertil Steril, 2007. **87**(4): p. 976.e13-5.
19. Nelson, D., et al., *Virilization in two pre-pubertal children exposed to topical androgen.* J Pediatr Endocrinol Metab, 2013. **26**(9-10): p. 981-5.
20. Cavender, R.K. and M. Fairall, *Precocious puberty secondary to topical testosterone transfer: a case report.* J Sex Med, 2011. **8**(2): p. 622-6.
21. Satonin, D.K., et al., *Amount of Testosterone on Laundered Clothing After Use of Testosterone Topical 2% Solution by Healthy Male Volunteers.* J Sex Med, 2016. **13**(2): p. 187-93.
22. USFDA, A., *Compounding Quality Act, Title I of the Drug Quality and Security Act.* 2013.
23. Samplaski, M.K., et al., *Testosterone use in the male infertility population: prescribing patterns and effects on semen and hormonal parameters.* Fertil Steril, 2014. **101**(1): p. 64-9.
24. Corona, G., et al., *Different testosterone levels are associated with ejaculatory dysfunction.* J Sex Med, 2008. **5**(8): p. 1991-8.
25. Rastrelli, G., et al., *Factors affecting spermatogenesis upon gonadotropin-replacement therapy: a meta-analytic study.* Andrology, 2014. **2**(6): p. 794-808.

26. Organization, W.H., *Contraceptive efficacy of testosterone-induced azoospermia and oligozoospermia in normal men.* Fertil Steril, 1996. **65**(4): p. 821-9.
27. Coviello, A.D., et al., *Low-dose human chorionic gonadotropin maintains intratesticular testosterone in normal men with testosterone-induced gonadotropin suppression.* J Clin Endocrinol Metab, 2005. **90**(5): p. 2595-602.
28. Medras, M., et al., *Breast cancer and long-term hormonal treatment of male hypogonadism.* Breast Cancer Res Treat, 2006. **96**(3): p. 263-5.
29. Thomas, S.R., et al., *Invasive breast cancer after initiation of testosterone replacement therapy in a man--a warning to endocrinologists.* Endocr Pract, 2008. **14**(2): p. 201-3.
30. Sorscher, S., *54-year-old man with breast cancer after prolonged testosterone therapy.* Clin Adv Hematol Oncol, 2005. **3**(9): p. 713.
31. Kaufman, J.M. and R.J. Graydon, *Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men.* J Urol, 2004. **172**(3): p. 920-2.
32. Agarwal, P.K. and M.G. Oefelein, *Testosterone replacement therapy after primary treatment for prostate cancer.* J Urol, 2005. **173**(2): p. 533-6.
33. Khera, M., et al., *Testosterone replacement therapy following radical prostatectomy.* J Sex Med, 2009. **6**(4): p. 1165-1170.
34. Pastuszak, A.W., et al., *Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy.* J Urol, 2013. **190**(2): p. 639-44.
35. Bhasin, S., et al., *Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline.* J Clin Endocrinol Metab, 2010. **95**(6): p. 2536-59.
36. Kathrins, M., et al., *The Relationship Between Testosterone-Replacement Therapy and Lower Urinary Tract Symptoms: A Systematic Review.* Urology, 2016. **88**: p. 22-32.
37. Debruyne, F.M., et al., *Testosterone treatment is not associated with increased risk of prostate cancer or worsening of lower urinary tract symptoms: prostate health outcomes in the Registry of Hypogonadism in Men.* BJU Int, 2017. **119**(2): p. 216-224.
38. Jiang, X.I., et al., *Clinical significance and expression of microRNA in diabetic patients with erectile dysfunction.* Exp Ther Med, 2015. **10**(1): p. 213-218.
39. Shi, M.D., et al., *The connection between type 2 diabetes and erectile dysfunction in Taiwanese aboriginal males.* Int J Impot Res, 2014. **26**(6): p. 235-40.
40. Abou-Seif, M.A. and A.A. Youssef, *Oxidative stress and male IGF-1, gonadotropin and related hormones in diabetic patients.* Clin Chem Lab Med, 2001. **39**(7): p. 618-23.
41. Corona, G., et al., *Association of hypogonadism and type II diabetes in men attending an outpatient erectile dysfunction clinic.* Int J Impot Res, 2006. **18**(2): p. 190-7.

42. Corona, G., et al., *Type 2 diabetes mellitus and testosterone: a meta-analysis study.* Int J Androl, 2011. **34**(6 Pt 1): p. 528-40.
43. Svartberg, J., et al., *The associations of endogenous testosterone and sex hormone-binding globulin with glycosylated hemoglobin levels, in community dwelling men. The Tromso Study.* Diabetes Metab, 2004. **30**(1): p. 29-34.
44. Kapoor, D., et al., *Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes.* Eur J Endocrinol, 2006. **154**(6): p. 899-906.
45. 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**(6): p. 725-33.
46. Arver, S., et al., *Serum dihydrotestosterone and testosterone concentrations in human immunodeficiency virus-infected men with and without weight loss.* J Androl, 1999. **20**(5): p. 611-8.
47. Slama, L., et al., *Longitudinal Changes Over 10 Years in Free Testosterone Among HIV-Infected and HIV-Uninfected Men.* J Acquir Immune Defic Syndr, 2016. **71**(1): p. 57-64.
48. Rietschel, P., et al., *Prevalence of hypogonadism among men with weight loss related to human immunodeficiency virus infection who were receiving highly active antiretroviral therapy.* Clin Infect Dis, 2000. **31**(5): p. 1240-4.
49. Crum-Cianflone, N.F., et al., *Erectile dysfunction and hypogonadism among men with HIV.* AIDS Patient Care STDS, 2007. **21**(1): p. 9-19.
50. Gomes, A.R., et al., *Prevalence of testosterone deficiency in HIV-infected men under antiretroviral therapy.* BMC Infect Dis, 2016. **16**(1): p. 628.
51. Cohan, G.R., *HIV-associated hypogonadism.* AIDS Read, 2006. **16**(7): p. 341-5, 348, 352-4.
52. Rochira, V., et al., *Premature decline of serum total testosterone in HIV-infected men in the HAART-era.* PLoS One, 2011. **6**(12): p. e28512.
53. Holmegard, H.N., et al., *Endogenous sex hormones and risk of venous thromboembolism in women and men.* J Thromb Haemost, 2014. **12**(3): p. 297-305.
54. Black, A.M., A.G. Day, and A. Morales, *The reliability of clinical and biochemical assessment in symptomatic late-onset hypogonadism: can a case be made for a 3-month therapeutic trial?* BJU Int, 2004. **94**(7): p. 1066-70.
55. Haddad, R.M., et al., *Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials.* Mayo Clin Proc, 2007. **82**(1): p. 29-39.
56. Calof, O.M., 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**(11): p. 1451-7.

57. Ponce, O.J., et al., *The efficacy and adverse events of testosterone replacement therapy in hypogonadal men: A systematic review and meta-analysis of randomized, placebo-controlled trials.* J Clin Endocrinol Metab, 2018.
58. Palacios, A., et al., *Effect of testosterone enanthate on hematopoiesis in normal men.* Fertil Steril, 1983. **40**(1): p. 100-4.
59. Ajayi, A.A., R. Mathur, and P.V. Halushka, *Testosterone increases human platelet thromboxane A2 receptor density and aggregation responses.* Circulation, 1995. **91**(11): p. 2742-7.
60. Baillargeon, J., et al., *Risk of Venous Thromboembolism in Men Receiving Testosterone Therapy.* Mayo Clin Proc, 2015. **90**(8): p. 1038-45.
61. Martinez, C., et al., *Testosterone treatment and risk of venous thromboembolism: population based case-control study.* Bmj, 2016. **355**: p. i5968.
62. Saad, F., et al., *Onset of effects of testosterone treatment and time span until maximum effects are achieved.* Eur J Endocrinol, 2011. **165**(5): p. 675-85.
63. Braekkan, S.K., et al., *Hematocrit and risk of venous thromboembolism in a general population. The Tromso study.* Haematologica, 2010. **95**(2): p. 270-5.
64. Carter, H.B., et al., *Early detection of prostate cancer: AUA Guideline.* J Urol, 2013. **190**(2): p. 419-26.
65. Behre, H.M., J. Bohmeyer, and E. Nieschlag, *Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls.* Clin Endocrinol (Oxf), 1994. **40**(3): p. 341-9.