Controversies and Advances With Testosterone Therapy: A 40-Year Perspective

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Testosterone therapy (TTh) has become highly controversial. There are important health consequences of testosterone deficiency, and meaningful benefits with treatment. There is level 1 evidence that TTh improves sexual function and desire, body composition, and bone density. Concerns regarding cardiovascular risk were based on two deeply flawed retrospective studies and are contradicted by dozens of studies showing cardiovascular benefits of TTh or higher endogenous testosterone, including placebo-controlled studies in men with known heart disease (angina, heart failure). Prostate cancer should no longer be considered a risk of TTh. Testosterone is neither scourge nor panacea—it is just good medicine. UROLOGY 89: 27–32, 2016. © 2016 Elsevier Inc.

"We must seek the truth like a lost child seeks its mother"
Old rabbinical saying

After nearly 40 years working with testosterone (T)—first, as a basic science researcher and, for the last 27 years, as a clinician and investigator—I have been a witness to a considerable number of advances and controversies in the diagnosis and management of testosterone deficiency (TD), also known as hypogonadism. I have been honored to be able to contribute to the field, particularly in the understanding of the biological relationship of androgens to prostate cancer (PCa). As physicians and the public have come to increasingly recognize the benefits of testosterone therapy (TTh), there has also developed a powerful backlash against the use of TTh. Today, the topic of TTh generates as much passion as any other topic in medicine.

Unfortunately, passion makes dispassionate analysis impossible. Today, there is a dominant narrative that the benefits of TTh are unproven, the risks are substantial, and TTh is abused and overused because of physicians yielding to unwarranted demand by misguided patients who are unwilling to accept normal aging. Although there is no evidence to support this position, and considerable evidence to the contrary, this narrative has trumped the facts within the public media. The impact of this vilification of TTh has been substantial, discouraging symptomatic patients from accepting a potentially beneficial treatment, and generating suspicion of physicians offering TTh by their colleagues, for questionable medical practices. This is unfair to patients and physicians alike.

Once a narrative is established, it influences how we view new information.[1] For example, it has been reported that rates of absent T testing prior to receiving a T prescription are approximately 25%.[2] This high rate of absent testing has been interpreted to indicate that there is widespread prescription of TTh that is inappropriate. However, the same methodology also revealed absent testing prior to TTh prescription by nearly 20% of endocrinologists, based on computerized data without a single medical chart being examined.[3] It is not credible that this high value is accurate because endocrinologists are trained to evaluate patients based on serum hormone levels, and testosterone blood tests are easily available throughout the US, yet we willingly accept the unlikely conclusion of inappropriate T prescribing because we have been predisposed to believe it is true. We must recognize our own biases in order to objectively assess evidence. Below, I present information regarding several of the key topics in TTh today.

TERMINOLOGY

TD is now increasingly preferred over the older term, hypogonadism, to describe the clinical syndrome in which low levels of testosterone lead to clinical signs and symptoms. Hypogonadism technically refers also to the impaired testicular production of sperm, which is not of immediate relevance to most men with low testosterone levels. For this reason, TD is considered simpler and more accurate than hypogonadism and is the terminology used in this review. TTh is preferred over testosterone replacement therapy for similar reasons, as testosterone is not "replaced" in men, unlike hormone replacement therapy in women.

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HISTORY

Testosterone was first synthesized in the mid-1930s, and underwent a brief golden period, being described in *New England Journal of Medicine* in several papers in the late 1930s and early 1940s as a potent treatment for impotence, lassitude, muscle strength, restoration of secondary sexual characteristics, and mood among hypogonadal men, and also as a successful treatment for angina.[4,5] However, concerns that testosterone "activated" prostate cancer soon trumped this early enthusiasm.[6] By the time that I began my urological practice in 1988, the use of TTh was rare and restricted to the most severe cases, such as men with pituitary tumors or anorchia.

I was curious about the role of T based on research I had performed in the American chameleon, *Anolis carolinensis*, beginning in the mid-1970s.[7] Those experiments demonstrated that T had important activity in the brain that was sufficient to restore sexual behavior in the castrated male. I therefore began routinely obtaining testosterone levels in my patients with sexual or reproductive issues, and was surprised at the high prevalence of low T levels in these men. I was even more surprised when a large majority of these men responded well to T injections, not only with improved or resolved sexual complaints but also with reports of improved energy, decreased fatigue, and improved mood and sense of well-being. TTh became a standard part of my treatment for T-deficient men with sexual dysfunction in the early 1990s, at a time when research was focused nearly entirely on vascular etiologies and treatments for erectile dysfunction (ED).

The approval of the first topical gel, AndroGel, in 2000, exposed a much broader physician population to the potential benefits of TTh. This coincided with public interest in quality of life and a wish to minimize symptoms that had previously been considered inevitable consequences of aging. Today, there are 21 approved T formulations in the US. As use has gone up, so has the level of scrutiny and the number of critical media stories. Many of these have been anchored by reports of increased cardiovascular (CV) risk that were published approximately 2 years ago.[8,9]

BENEFITS OF TTh

The frequently stated assertion that the benefits of TTh are unproven is simply false. There is level 1 evidence that TTh improves erection quality, libido, sexual frequency; increased lean mass and bone density; improves lipid parameters; causes reduced fat mass; and improves glycemic control.[10,11]

The sexual benefits of TTh are of particular importance because the chief presenting complaint that drives men with TD to see medical attention is sexual dysfunction. In a meta-analysis of randomized control trials (RCTs), TTh was shown to significantly improve libido in men with TT <8 nm/L (approximately 240 ng/dl) and TT <12 nm/L (approximately 350 ng/dl). Improvement in erection was also noted for these men with baseline T values below these same thresholds.[11] Importantly, eugonadal men did not demonstrate increased libido or erectile function. Significant improvements in frequency of sexual activity and orgasm were also noted.

There are mixed results for the use of TTh in addition to phosphodiesterase type 5 (PDE5) inhibitors for the treatment of ED. Improvement in erection was noted in uncontrolled studies but not in placebo-controlled studies.[11] This discrepancy may not only be due to the limitations of uncontrolled studies, but may also be related to the methodology of RCTs. For example, in the RCT by Spitzer et al, T-deficient men with ED were first treated with an interval of sildenafil, followed by the addition of a T gel.[12] Erections improved significantly during the PDE5i period, without additional benefit from TTh. However, the improvement in erection was so robust with PDE5i alone that there was little opportunity to demonstrate additional benefit from TTh. Studies of this type are unable to answer the important clinical question whether TTh offers benefits for those men who fail PDE5i's. Anecdotally, in our practice we routinely offer TTh to men who fail PDE5i's, and often see positive responses.

WHO IS A CANDIDATE FOR TTh?

There is consensus that candidates for treatment with TTh should have signs or symptoms of TD combined with biochemical evidence of low T levels.[13] The challenge, however, is deciding what T level is considered low. For the first 40 years after the commercial availability of T products, the diagnosis was made entirely on clinical presentation. With the introduction of readily available testing with the development of radioimmunoassays in the 1970s, the emphasis shifted to documentation of low blood levels. Today, it is becoming increasingly clear that symptoms and clinical presentation should once again take priority,[13] with blood test results an important, yet secondary confirmation.

The difficulty with arriving at a reasonable threshold value for biochemical confirmation of TD is underscored by the wide range of recommended thresholds offered by various professional groups and experts, ranging from 200 ng/dl (approximately 7 nmol/l) to 400 ng/dl (approximately 14 nmol/l).[13] This confusing situation is worsened by the recommendation by the Endocrine Society in 2010 to follow reference ranges provided by the laboratory performing the testosterone testing,[14] because there is so much variation in reference ranges across laboratories that one survey revealed that 17 of 25 laboratories had different reference ranges.[15] This means that the same test result may be categorized as normal by one laboratory and low by another.

The explanation for the wide range in threshold recommendations is that there is no specific T value that reliably separates men who may benefit from treatment from those who will not.[14] Threshold recommendations are therefore arbitrary. The application of lower thresholds means that a higher rate of treated men are likely to experience benefits, but at the cost of denying treatment to many men who may also benefit. Higher thresholds allow for inclusion of more candidates who may benefit, yet overall response rates may be lower.[16] Moreover, there is a substantial

degree of inter-individual variability with regard to symptoms and response to treatment, due at least, in part, to two known confounders—the binding of androgen to sex hormone binding globulin and genetic variability with regard to the number of CAG repeats in the androgen receptor gene, with larger numbers of repeats associated with reduced sensitivity.[17] This means that healthcare providers must decide on whether a course of treatment is indicated based on the totality of clinical presentation rather than by a blood test result alone.

In our practice, we have found free testosterone to be more clinically useful than total testosterone, as it is independent of sex hormone binding globulin variability.[18] Values <1.5 ng/dl for direct free T measurement or <100 pg/ml for calculated free T are consistent with a diagnosis of TD in symptomatic men.[16,19] We routinely measure both total and free testosterone during the evaluation and also to monitor response to treatment.

The current widespread practice by health insurance companies, including Medicare, to restrict coverage based on specific testosterone threshold values therefore lacks a scientific basis and is contrary to good medical practice. The diagnosis of TD requires clinical judgment, and attempts to replace this with irrational adherence to arbitrarily selected values prevent healthcare providers from offering important treatments to appropriately selected patients.

TESTOSTERONE AND PROSTATE CANCER

Until recently, the greatest concern regarding TTh among physicians has been the risk of PCa.[20] This concern was based on the androgen hypothesis, which posited that ever-greater androgen concentrations led to ever-greater PCa risk and growth.[21] Arguably, the greatest advancement in the field of T therapy over the last twenty years has been the conceptual revolution regarding the relationship of androgens to PCa. Today, the androgen hypothesis can no longer be seriously considered as it is contradicted by a substantial body of evidence.[22] It has been replaced by the saturation model, which describes an exquisite sensitivity to changes in serum androgen concentrations at very low androgen concentrations, and an indifference to changes at higher concentrations.[21] The saturation model was originally described in 2006 to explain the varied responses to androgens by prostate tissue, benign and malignant, and has since been developed further[23] and confirmed by additional observations.

Although androgen deprivation results in dramatic changes in PSA, and increased serum T causes a rise in PSA in men with castrate-level T concentrations, there is also strong evidence that there is a limit to the ability of androgens to stimulate prostate growth, with a maximum reached at low serum T concentrations.[23] Serum PSA in cross-sectional studies is independent of serum T.[24] Administration of supraphysiologic doses of T in healthy volunteers resulted in no increase in PSA or prostate volume for periods up to 9 months.[25] Androgen-sensitive PCa cell lines demonstrate greater growth with increasing androgen concentrations, followed by stabilization and then growth inhibition as androgen concentrations are increased further.[26]

Clinical support for the saturation model comes from the observation in two studies that T therapy was associated with a significant rise in PSA for men with baseline serum T less than 250 ng/dl, but no increase was observed in men with baseline T above 250 ng/dl.[27,28] In addition, Rastrelli et al demonstrated a naturally occurring saturation curve in 2967 men, with a saturation point of approximately 250 ng/dl.[29] These results are consistent with studies demonstrating maximal androgen receptor binding of androgen in vitro at concentrations consistent with these values in vivo.[30] Finally, Marks et al showed that intra-prostatic concentrations of T and dihydrotestosterone failed to increase significantly with T therapy, despite large increases in serum T, suggesting alternative mechanisms by which a maximal androgenic effect may be achieved.[31]

The importance of the saturation model is that it provides a theoretical foundation for the relatively new practice of offering TTh to selected men with PCa. Although there are no controlled studies to date to offer definitive assessment of risk, a moderate number of case series have demonstrated minimal risk of PCa recurrence or progression with T therapy beyond what would be expected without T therapy.[32] This includes series of men who received T therapy after RP,[33] after brachytherapy,[34] and after various forms of radiation.[35] In 2011, Morgentaler et al reported the use of T therapy in 13 men on active surveillance for PCa.[36] After a median of 2 years of TTh, none demonstrated progression of PCa. More recently, Kacker et al compared progression rates with TTh in 28 men on active surveillance compared with a similar group of 96 men with untreated TD who did not receive TTh.[37] No difference in progression rates was observed. T therapy in men with a history of PCa remains controversial, yet it is important to recognize that the prohibition against this practice was not based on evidence but on the now-discredited androgen hypothesis. Recommendations for case selection appear in the review by Khera et al.[32]

DOES HIGH ENDOGENOUS T OR TTh INCREASE THE RISK OF PCa?

In 2004, my fellow, Ernani Rhoden, and I published the first in-depth analysis of the risk of TTh with regard to PCa.[38] Until that time, it was axiomatic that higher T concentrations predisposed men to PCa development and growth. We were therefore stunned to discover that we were unable to find any solid evidence that higher endogenous T levels or TTh itself were associated with increased risk of PCa or of high-grade PCa. More recent evidence confirms this. A prospective longitudinal study involving 3886 men with PCa and 6448 age-matched controls showed no relationship between serum androgens and PCa risk.[39] In the placebo arm of the REDUCE trial, 3255 men underwent prostate biopsy at years 2 and 4, revealing no association between PCa risk and serum T or dihydrotestosterone.[40] In a meta-analysis of 22 RCTs involving 2351 men, those who received TTh were

at no greater risk of developing PCa compared with men who received placebo.[41] Recently, Baillargeon et al investigated the SEER database and reported that among 52,579 men with PCa, those with exposure to TTh were at no greater risk for high-grade PCa than untreated men.[42]

LOW T LEVELS ARE ASSOCIATED WITH WORSE PROGNOSIS FOR PCa

Remarkably, the weight of evidence today strongly indicates an association between *low* T levels and worse PCa disease and prognosis. In 1996, my colleagues and I reported PCa rates of 14% using sextant biopsies in men with low T and normal PSA and DRE, a rate similar to men known to be at increased risk based on elevated PSA of 4-10 ng/ml.[43] Subsequent studies have shown that low T levels are associated with higher Gleason score, greater stage at RP, increased SV involvement, higher biochemical recurrence rates, and reduced survival.[32] In a cohort of men undergoing active surveillance, low values of free T were found to be an independent predictor of progression.[44]

CARDIOVASCULAR RISK

In November 2013 and January 2014, two retrospective studies reported increased CV risks associated with T prescriptions.[8,9] This message was amplified in the US by television ads by plaintiff attorneys seeking cases for class action lawsuits. Health Canada and the FDA announced concerns and added new warnings regarding CV risk with TTh products. In addition, the FDA announced a new warning regarding the risk of venous thromboembolic events.

These reports of increased risk were surprising to experts in the field, since there had been accumulating evidence over two decades that higher levels of endogenous T appeared to be protective against CV risk, and TTh had been shown to be associated with reduced mortality and clear evidence of improved CV risk factors, such as fat mass and glycemic control.[45] These two articles reporting risks merit closer inspection, since they received so much media attention and anchored many critical commentaries on the use of TTh, despite the fact that their findings ran counter to a large body of evidence.

The first of these, by Vigen et al,[8] was a retrospective study of 8709 men in the VA healthcare system who underwent coronary angiography and had T levels <300 ng/dl. Some of these men eventually received a prescription for TTh, and the rest went untreated. The authors reported that the absolute rate of adverse events [cumulative for stroke, myocardial infarction (MI), and death] was 25.7% in the T-treated group and only 19.9% in the untreated group. However, these results were misreported. The correct absolute rate of events was *lower by half* in the T-treated group compared with the untreated group, at 10.1% and 21.2%, respectively.[46] The article was subsequently revised to change "absolute rate of events" to "estimated cumulative probability of events" based on adjustment for 54 factors. This fundamental error was not noted in the media. A second major error was discovered several months later, when the journal published a second correction revealing the authors had made an error involving more than 1000 men, and discovered that their all-male population was contaminated by nearly 10% women.[47] More than 160 leading scientific figures and 29 medical societies have called for retraction of the article, concluding that these errors rendered the results "no longer credible".[48]

The second article, by Finkle et al,[9] was an analysis of a large insurance database. The authors reported a 36% increase in nonfatal MI in the 90 days following receipt of a T prescription compared with the 12 months prior to the prescription. There was no control group, so it is unknown whether untreated men with TD would have had a higher, lower, or similar rate of MI. In addition, the comparison of the two periods is invalid, since the retrospective nature of this study means that the 12-month period prior to the prescription represents how often physicians were willing to prescribe TTh to men with a recent MI, rather than representing a true rate of MI. It makes no sense to compare physician prescription patterns with true MI rates following receipt of the prescription. Importantly, the actual rate of MI following a T prescription was very low, at approximately one-third the expected MI rate using the NIH Heart Attack Calculator.[45]

In contrast, several dozen articles strongly suggest that *low* levels of T represent a risk factor for CV disease and mortality, and that T administration may be beneficial or protective (reviewed in Ref. 45). In particular, the literature demonstrates that *low* T levels are associated with increased mortality, atherosclerosis, incident coronary artery disease, severity of coronary artery disease, and carotid plaque or intima-media thickness. In two observational studies of T-deficient men, mortality was reduced by half among men that received T therapy compared with untreated men. In addition, several RCTs in men with known heart disease have shown improved exercise capacity with TTh compared with placebo. This has been shown in men with angina and in men (and one study in women) with heart failure.

Finally, TTh has been shown to improve known CV risk factors, such as reducing fat mass, resolving the metabolic syndrome, and improving glycemic control.

Recently, Sharma et al investigated 83,010 men with documented low T levels, and categorized them into three groups.[49] Group 1 received T therapy with normalization of T levels, group 2 received T therapy but failed to achieve normalized T levels, and group 3 did not receive T therapy. Results revealed that all-cause mortality, MI, and stroke were all significantly reduced in men who achieved normalization of T levels compared with men who did not receive TTh, or who did not achieve normalization. Importantly, those in group 2 (inadequate TTh) had no greater risk of stroke or MI than untreated men in group 3.

In summary, there appears to be no solid evidence supporting the concern that TTh is associated with increased CV risk. On the contrary, there is an as yet underappreciated

awareness that TD itself increases CV risk, and that treatment is associated with CV benefits, especially in at-risk populations. In addition, the first large-scale study of venous thromboembolism risk with TTh has now been published, revealing no increased rate of venous thromboembolism among men who received a T prescription.[50] It is a peculiarity of our time that these rare studies reporting increased risk receive considerably more media attention than the numerous studies reporting reassuring results.

FUTURE DIRECTIONS

Over the course of its history, the value of TTh has been tainted: first by its implication with PCa, and more recently with concerns regarding CV risk. Yet as these concerns fade, there are a number of areas where current and future research may provide important clinical advances with TTh. One group recently reported phase 1 data in which men with metastatic castrate-resistant PCa were treated to monthly cycles of intermittently high-dose T injections followed by extremely low T levels due to androgen deprivation.[51] Positive clinical responses were noted in several men, providing a rationale for considering the possibility that TTh may have a future role in the treatment of PCa.

Substantial data have accumulated that TTh improves body composition and glycemic control in obese or diabetic men with TD. An observational study over 5 years showed remarkable progressive improvement in waist circumference and weight of men who received long-acting T injections.[52] Given the relative ineffectiveness of nonsurgical treatments for obesity, it may be that TTh will have a future role in weight loss management, if these findings are supported by prospective, controlled studies.

Perhaps most importantly, the current controversy regarding possible CV risks with TTh has led to the recent publication of a number of observational studies that suggest there may be a protective benefit of TTh with regard to CV events, including MI, stroke, and mortality.[49,53] The implications of this for future generations are substantial, but will require the performance of a very large prospective trial over several years.

DISCUSSION

The advantage of spending many years in a field is that one develops an appreciation for the ebb and flow of medical and scientific opinion. Testosterone has always been controversial, based on its designation as "the male hormone," and its promotion in some quarters as an antiaging tonic. The ubiquitous advertising by for-profit clinics and especially by supplement companies making over-the-top claims have created a reactionary atmosphere where a skeptical public, including physicians, is ready to seize upon negative stories that suggest there is something wrong with TTh. It is thus curious, but not altogether surprising, that just as the fear of prostate cancer is waning, we find ourselves concerned with a new "crisis" related to testosterone, namely, CV risk. There is no good evidence for either of these, yet once a dominant narrative has been established, it can be exceedingly difficult to return to an objective stance where the evidence again becomes paramount.

If one examines the evidence dispassionately, what is clear is that TD creates important medical and quality of life issues for men. Symptoms that arise from a deficiency of T will respond nicely to treatment. For some men, treatment can be experienced as life changing. Others will describe the benefits as solid. Some men will not respond at all even after a reasonable trial of treatment, which can be considered 3-6 months with T levels in the upper third of the normal range. In these cases, TTh may be discontinued.

The risks of TTh include erythrocytosis, peripheral edema, acne, breast tenderness or enlargement, and testicular atrophy. Men must be questioned whether they wish to preserve fertility, since treatment with exogenous T reduces sperm concentrations, often to zero.

The most difficult decision for clinicians is to determine who to treat. In general, the likelihood of benefit is greater for those with more severe degrees of TD, yet there is enormous interindividual variability for any given T level with regard to symptoms and to response to treatment. This means that there is an important role for the "art" of medicine in decision-making regarding TTh. Men are not defined by their T values. The clinical presentation is most important. The denial of healthcare coverage by insurance companies based on requirements to meet specific T thresholds is unscientific and replaces clinical judgment with an arbitrary threshold for an imprecise test. This is a transplant attempt by health insurance companies to deny treatment and thereby reduce costs. This practice should be condemned.

After 40 years in the field, this is what I see. TTh for men with TD is neither a panacea nor a scourge. It is simply good medicine.

References

1. Morgentaler A. Testosterone, cardiovascular risk, and hormonophobia. *J Sex Med.* 2014;11:1362-1366.
2. Baillargeon J, Urban RJ, Ottenbacher KJ, Pierson KS, Goodwin JS. Trends in androgen prescribing in the United States, 2001 to 2011. *JAMA Intern Med.* 2013;173:1465-1466.
3. Baillargeon J, Urban RJ, Kuo YF, et al. Screening and monitoring in men prescribed testosterone therapy in the U.S., 2001-2010. *Public Health Rep.* 2015;130:143-152.
4. Aub JC. Reports on medical progress. Endocrines: the use of testosterone. *N Engl J Med.* 1940;222:877-881.
5. Lesser MA. The treatment of angina pectoris with testosterone propionate- preliminary report. *N Engl J Med.* 1942;226:51-54.
6. Huggins C, Hodges CV. The effect of castration, of estrogen and of androgen injection on serum phosphatase on metastatic carcinoma of the prostate. *Cancer Res.* 1941;1:293-297.
7. Morgentaler A, Crews D. Role of the anterior hypothalamus-preoptic area in the regulation of reproductive behavior in the lizard, anolis carolinensis: implantation studies. *Horm Behav.* 1978;11:61.
8. Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA.* 2013;310:1829-1836.
9. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of nonfatal myocardial infarction following testosterone therapy prescription in men. *PLoS ONE.* 2014;9:e85805.

10. Isidori AM, Balercia G, Calogero AE, et al. Outcomes of androgen replacement therapy in adult male hypogonadism: recommendations from the Italian society of endocrinology. *J Endocrinol Invest*. 2015;38:103-112.
11. Corona G, Isidori AM, Buvat J, et al. Testosterone supplementation and sexual function: a meta-analysis study. *J Sex Med*. 2014;11:1577-1592.
12. Spitzer M, Basaria S, Travison TG, et al. Effect of testosterone replacement on response to sildenafil citrate in men with erectile dysfunction: a parallel, randomized trial. *Ann Intern Med*. 2012;157:681-691.
13. Morgentaler A, Khera M, Maggi M, Zitzmann M. Commentary: who is a candidate for testosterone therapy? A synthesis of international expert opinions. *J Sex Med*. 2014;11:1636-1645.
14. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010;95:2536-2559.
15. Lazarou S, Reyes-Vallejo L, Morgentaler A. Wide variability in laboratory reference values for serum testosterone. *J Sex Med*. 2006;3:1085-1089.
16. Aversa A, Morgentaler A. The practical management of testosterone deficiency in men. *Nat Rev Urol*. 2015;12:641-650.
17. Zitzmann M. The role of the CAG repeat androgen receptor polymorphism in andrology. *Front Horm Res*. 2009;37:52-61.
18. Kacker R, Hornstein A, Morgentaler A. Free testosterone by direct and calculated measurement versus equilibrium dialysis in a clinical population. *Aging Male*. 2013;16:164-168.
19. Morgentaler A. Commentary: guideline for male testosterone therapy: a clinician's perspective. *J Clin Endocrinol Metab*. 2007;92:416-417.
20. Gooren LJ, Behre HM. Diagnosing and treating testosterone deficiency in different parts of the world: changes between 2006 and 2010. *Aging Male*. 2012;15:22-27.
21. Morgentaler A. Testosterone and prostate cancer: an historical perspective on a modern myth. *Eur Urol*. 2006;50:935-939.
22. Morgentaler A. Goodbye androgen hypothesis, hello saturation model. *Eur Urol*. 2012;62:765-767.
23. Morgentaler A, Traish A. Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. *Eur Urol*. 2009;55:310-320.
24. Monath JR, McCullough DL, Hart LJ, Jarow JP. Physiologic variations of serum testosterone within the normal range do not affect serum prostate-specific antigen. *Urology*. 1995;46:58-61.
25. Cooper CS, Perry PJ, Sparks AE, et al. Effect of exogenous testosterone on prostate volume, serum and semen prostate specific antigen levels in healthy young men. *J Urol*. 1998;159:441-443.
26. Song W, Khera M. Physiological normal levels of androgen inhibit proliferation of prostate cancer cells in vitro. *Asian J Androl*. 2014;16:864-868.
27. Morgentaler A, Benesh JA, Denes BS, Kan-Dobrosky N, Harb D, Miller MG. Factors influencing prostate-specific antigen response among men treated with testosterone therapy for 6 months. *J Sex Med*. 2014;11:2818-2825.
28. Khera M, Bhattacharya RK, Blick G, et al. Changes in prostate specific antigen in hypogonadal men after 12 months of testosterone replacement therapy: support for the prostate saturation theory. *J Urol*. 2011;186:1005-1011.
29. Rastrelli G, Corona G, Vignozzi L, et al. Serum PSA as a predictor of testosterone deficiency. *J Sex Med*. 2013;10:2518-2528.
30. Traish AM, Williams DF, Hoffman ND, Wotiz HH. Validation of the exchange assay for the measurement of androgen receptors in human and dog prostates. *Prog Clin Biol Res*. 1988;262:145-160.
31. Marks LS, Mazer NA, Mostaghel E, et al. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. *JAMA*. 2006;296:2351-2361.
32. Khera M, Crawford D, Morales A, Salonia A, Morgentaler A. A new era of testosterone and prostate cancer: from physiology to clinical implications. *Eur Urol*. 2014;65:115-123.
33. Pastuszak AW, Pearlman AM, Lai WS, et al. Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. *J Urol*. 2013;190:639-644.
34. Balbontin FG, Moreno SA, Bley E, Chacon R, Silva A, Morgentaler A. Long-acting testosterone injections for treatment of testosterone deficiency after brachytherapy for prostate cancer. *BJU Int*. 2014;114:125-130.
35. Pastuszak AW, Khanna A, Badhiwala N, et al. Testosterone therapy after radiation therapy for low, intermediate and high risk prostate cancer. *J Urol*. 2015;194:1271-1276.
36. Morgentaler A, Lipshultz LI, Avila D Jr, Bennett R, Sweeney M, Khera M. Testosterone therapy in men with untreated prostate cancer. *J Urol*. 2011;185:1256-1261.
37. Kacker R, Mariam H, San Francisco IF, et al. Can testosterone therapy be offered to men on active surveillance for prostate cancer? Preliminary results. *Asian J Androl*. 2015;doi:10.4103/1008-682X.160270.
38. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. *N Engl J Med*. 2004;350:482-492.
39. Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *J Natl Cancer Inst*. 2008;100:170-183.
40. Muller RL, Gerber L, Moreira DM, et al. Serum testosterone and dihydrotestosterone and prostate cancer risk in the placebo arm of the reduction by dutasteride of prostate cancer events trial. *Eur Urol*. 2012;62:757-764.
41. Cui Y, Zong H, Yan H, Zhang Y. The effect of testosterone replacement therapy on prostate cancer: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis*. 2014;17:132-143.
42. Baillargeon J, Kuo YF, Fank X, Shahinian VB. Long-term exposure to testosterone therapy and the risk of high grade prostate cancer. *J Urol*. 2015;194:1612-1616.
43. Morgentaler A, Bruning CO III, DeWolf WC. Incidence of occult prostate cancer among men with low total or free serum testosterone. *JAMA*. 1996;276:1904-1906.
44. San Francisco IF, Rojas PA, DeWolf WC, Morgentaler A. Low free testosterone levels predict disease reclassification in men with prostate cancer undergoing active surveillance. *BJU Int*. 2014;114:229-235.
45. Morgentaler A, Miner MM, Caliber M, Guay AT, Khera M, Traish AM. Testosterone therapy and cardiovascular risk: advances and controversies. *Mayo Clin Proc*. 2015;90:224-251. [Epub Jan 27, 2015].
46. Traish AM, Guay AT, Morgentaler A. Death by testosterone? We think not! *J Sex Med*. 2014;11:624-629.
47. Vigen R, O'Donnell CI, Barón AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. [published correction "Correction: incorrect number of excluded patients reported in the text and figure" appears in JAMA. 2014;311:967]. *JAMA*. 2013;310:1829-1836.
48. Morgentaler A, Lunenfeld B. Testosterone and cardiovascular risk: world's experts take unprecedented action to correct misinformation. *Aging Male*. 2014;17:63-65.
49. Sharma R, Oni OA, Gupta K, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. *Eur Heart J*. 2015;36:2706-2715.
50. Baillargeon J, Kuo YF, Sharma G, et al. Risk of venous thromboembolism in men receiving testosterone therapy. *Mayo Clin Proc*. 2015;90:1038-1045.
51. Schweizer MT, Antonarakis ES, Wang H, et al. Effect of bipolar androgen therapy for asymptomatic men with castration-resistant prostate cancer: results from a pilot clinical study. *Sci Transl Med*. 2015;7:1138-1144. 269ra2.
52. Saad F, Haider A, Doros G, Traish A. Long-term treatment of hypogonadal men with testosterone produces substantial and sustained weight loss. *Obesity (Silver Spring)*. 2013;21:1975-1981.
53. Baillargeon J, Urban RJ, Kuo YF, et al. Risk of myocardial infarction in older men receiving testosterone therapy. *Ann Pharmacother*. 2014;48.