Commentary: Who Is a Candidate for Testosterone Therapy? A Synthesis of International Expert Opinions

Abraham Morgentaler, MD,* Mohit Khera, MD,† Mario Maggi, MD,‡ and Michael Zitzmann, MD, PhD§

*Men's Health Boston, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; †Baylor College of Medicine, Houston, TX, USA; ‡Sexual Medicine & Andrology, University of Florence, Florence, Italy; §Centre of Reproductive Medicine and Andrology/Clinical Andrology, University Clinics, Muenster, Germany

DOI: 10.1111/jsm.12546

ABSTRACT

Introduction. Despite increasing use of testosterone therapy (TTh) for men with testosterone deficiency (TD), there remains uncertainty determining who is a candidate for treatment.

Aim. The aim if this study was to report the opinions of international experts on TTh, as initially presented at the meeting of the World Meeting on Sexual Medicine in Chicago, United States in August 2012.

Methods. Expert responses to questions regarding the diagnosis of TD based on their own clinical and research experience.

Results. All experts emphasized the primacy of symptoms for the diagnosis of TD. Total testosterone (T) thresholds used to identify TD ranged from 350 ng/dL to 400 ng/dL (12–14 nmol/L); however, experts emphasized the diagnostic limitations of this test. Free T was obtained by all, with some valuing this test more than total T for clinical decision making. Only one expert routinely used a screening questionnaire. None used age-adjusted values. Bioavailable T and the free androgen index were not used. Luteinizing hormone (LH) and sex hormone-binding globulin levels were routinely obtained at evaluation. Additional supportive evidence for TD diagnosis included small testicular volume, high androgen receptor CAG repeats, elevated LH, and presence of diabetes or metabolic syndrome. Two T tests were generally obtained but not always required. Some experts did not require morning testing in men 50 years and older. All monitored prostate-specific antigen and hematocrit after initiation of TTh. All but one expert would consider a trial of TTh to a symptomatic man with total T within the normal range. Recent studies suggesting increased cardiovascular risk with T therapy were not found to be credible.

Conclusions. Determining who is a candidate for TTh requires clinical assessment based on symptoms and signs, with confirmatory laboratory evaluation. These expert opinions differed from some published guidelines by the emphasis on symptoms as paramount, recognition of the limitations of total T as a diagnostic test, and the potential utility of a therapeutic trial in symptomatic cases with normal total T concentrations. **Morgentaler A, Khera M, Maggi M, and Zitzmann M. Commentary: Who is a candidate for testosterone therapy? A synthesis of international expert opinions. J Sex Med **;**:**–**.**

Key Words. Testosterone; Hypogonadism; Treatment; Diagnosis; Evaluation; Monitoring

Introduction

Abraham Morgentaler, MD—In August 2012 at the World Meeting on Sexual Medicine in Chicago, I was honored to lead a postgraduate course entitled: Who is a candidate for testosterone therapy? The topic was chosen to address one of the most contentious and confusing aspects of testosterone therapy (TTh). An international panel of experts was selected as faculty, and each was asked to present his or her views and practices, based on their own extensive clinical experiences and androgen-related research interests. The expert panelists were Mario Maggi from

Italy, Michael Zitzmann from Germany, and Mohit Khera from the United States. The purpose of this report is to share the valuable perspectives of these expert clinician-researchers with the Journal readership.

Testosterone (T) has been available as a medical therapy since the 1930s; however, its use was limited until the last 10–15 years, at which point prescription rates began to increase at a rapid rate. This increase in TTh appears due to a combination of factors, including increased awareness of T deficiency (TD) (also known as hypogonadism or late-onset hypogonadism) as a treatable condition, the publication of numerous studies documenting benefits of TTh, decreased concern regarding safety risks, particularly prostate cancer, and the introduction of new commercial T formulations with associated marketing efforts. However, despite the long history of TTh, there has been little standardization regarding the evaluation and management of TD.

This lack of consensus causes confusion among clinicians and represents a significant hurdle impeding the appropriate use of TTh. The confusion stems from a number of factors: availability of multiple assays to determine androgen status, such as total, free, and bioavailable T, with proponents for each; widely differing laboratory reference ranges; limited clinical correlation between serum T concentrations and symptoms; and clinical experiences that differ from published guidelines.

Several expert groups and specialty societies have attempted to address these issues with published guidelines or recommendations. These include the Endocrine Society in the United States [1], joint guidelines on behalf of a number of international andrological societies [2], and recommendations from the International Consultation on Sexual Medicine [3].

With minor variations, those guidelines assert that the diagnosis of TD should only be made in men with characteristic symptoms or signs of TD in combination with a documented serum T that is low. In the 2006 version of the Endocrine Society guidelines [4], a serum T below 300 ng/dL (10.4 nmol/L) was set as the diagnostic threshold; however, in the 2010 updated version, clinicians were referred to their own laboratory's reference ranges [1]. Recommendations from the joint international societies indirectly support a threshold of 350 ng/dL (12 nmol/L) by asserting that men with serum T concentrations above this level generally do not benefit from treatment [2]. The International Consultation on Sexual Medicine repeats this threshold, but notes that treatment may be reasonably offered to symptomatic men with higher concentrations based on clinical judgment [3]. All groups recommend obtaining a second confirmatory total testosterone (TT) test prior to initiating treatment. The use of free or bioavailable T has been recommended by these groups only as a secondary test when serum T provides unclear results.

These guidelines provide a valuable guide for clinicians new to the field. However, guidelines have important limitations [5]. First, in the specific case of guidelines regarding T, each of the published documents acknowledges that the quality of supporting evidence for their major recommendations is poor. No studies have revealed any specific T concentration that reliably distinguishes men who will respond to treatment from men who will not.

Second, guidelines represent consensus documents created by groups of individuals, whose own practices may differ substantially from each other. As a result, final guidelines and recommendations may not reflect the actual clinical practice of any of the committee members. Third, guidelines have a tendency to produce recommendations that reflect "ideal" practices, which may differ from circumstances "on the ground" for the practicing clinician.

There is thus considerable value in learning how individual experts approach the problem of identifying candidates for TD. The practices of each of the experts contributing to this report have been honed by years of experience and informed by their own observations and research. Below are presented the questions and answers for each of the three panelists.

Questions and Answers

Q: How do you diagnose TD in your own practice? What symptoms, signs, and blood tests do you require in order to offer TTh?

Mohit Khera: I diagnose TD based on two criteria: low serum total or free T and signs or symptoms of TD. However, I must stress that in my practice, symptoms are the key driver for TTh rather than any specific value for blood test results.

In my experience, sexual symptoms such as low libido and erectile dysfunction (ED) are the most sensitive and specific symptoms. Many patients with TD also commonly present with fatigue, lack of energy, and reduced motivation. Because not all patients with TD present with sexual symptoms, I

also ask about depression, poor sleep, increased fat deposition, and decreased muscle mass.

I do not routinely use screening questionnaires because they have low specificity [2], although I will occasionally use the ADAM questionnaire to initiate a discussion regarding TD with my patients.

In deciding who is a candidate for T therapy, I tend to rely more on free T values than total T values, as I believe it offers a more accurate picture of T status in patients. I offer T therapy to symptomatic men with calculated free T less than 6.5 ng/dL (65 pg/mL or 232 pmol/L). I obtain a total T in all men and use this to calculate their free T. A total T value less than 400 ng/dL (14 nmol/L) in especially a younger man with hypogonadal symptoms would lead me to offer him TTh.

It is important to realize it is unknown below what T concentration threshold individuals develop symptoms of TD and adverse health outcomes. Moreover, it is clear that there are different thresholds at which various symptoms occur for any given individual and substantial differences between individuals. Although the 2010 Endocrine Society Guidelines state that "clinicians should use the lower limit of the normal range for healthy young men established in their laboratory" [1]. This approach is problematic because of substantial variability between laboratories and assays. Lazarou et al. queried 25 different laboratories and found that the lower limit of normal for total T varied from 130 ng/dL to 450 ng/dL, a 350% difference [6]. Thus, it is challenging to rigidly assign a lower limit of normal for free and total T based on our lack of scientific evidence, variability in laboratory reporting and assays, and variability between individuals.

Mario Maggi: In my clinical practice, I see male patients for three primary issues: delayed puberty, infertility, or sexual dysfunction. I check serum T in all of these men. I offer T therapy based on three considerations: (i) the nature of the hypogonadism; (ii) its clinical onset; and (iii) the patient's needs. Symptoms and signs in middle-aged or older men with TD have rather low specificity and sensitivity. The diagnosis of TD is often overlooked because the symptoms are relatively mild and insidious [7]. However, TD is often associated with metabolic comorbidities, such as type 2 diabetes mellitus (T2DM) and metabolic syndrome (MetS), and with increased overall and cardiovascular (CV) mortality. Signs and symptoms of TD for which I will consider treatment include: fatigue, depressed mood, and reduced bone density. The likelihood of TD is increased in the presence of reduced testis or prostate volumes as determined by physical examination, and increased waist circumference or pulse pressure [8]. The most strongly suggestive symptoms are reduced frequency of spontaneous erections, reduced sexual desire, reduced sexual frequency (including autoeroticism), reduced ejaculate volume, and increased time to reach orgasm.

We routinely use the ANDROTEST structured interview we developed in our evaluation of men with sexual dysfunction, with a 70% sensitivity and specificity in detecting low total or free T. However, it has been validated only in Italian men.

I routinely obtain the following blood tests in men suspected of TD: total and high-density lipoprotein cholesterol, HbA1c, fasting blood glucose, triglycerides, hematocrit/hemoglobin, prostate-specific antigen (PSA), luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, sex hormone-binding globulin (SHBG), and total T. The first five analytes are aimed to identify metabolic derangement that are often comorbid with (or determinant of) the TD. The last six analytes are useful to determine the existence and the nature of an eventual hypogonadal condition. In addition, hematocrit and PSA are useful not only to corroborate the diagnosis [9] but also as baseline value to monitor the efficacy of the T therapy. I consider treatment when total T is below 12 nmol/L (350 ng/dL) or calculated free T is below 225 pmol/L. However, if there is a metabolic derangement (e.g., MetS) or obesity, treating the underlying condition should be the first priority. In fact, removal and/or proper treatment of TD-associated comorbidities is essential in treating TD.

Michael Zitzmann: In my practice, symptoms are the key to the diagnosis of TD. The leading symptoms are loss of libido, ED, lack of energy, and depressed mood. Some patients report decreased physical abilities and changes in body composition, namely decreased muscle mass and increased body fat, but these do not usually prompt the medical consultation. TD is common in men with metabolic problems (i.e., obesity/T2DM). These men usually seek medical attention because of the same primary symptoms, including ED.

A second necessary step is the laboratory investigation. I consider total T levels below 12 nmol/L (350 ng/dL) indicative of TD. I also take calculated free T into consideration, particularly for men with total T between 8 nmol/L (230 ng/dL) and 12 nmol/L (350 ng/dL). Free T levels below

250 pmol/L (86 pg/mL) are highly suggestive of TD.

In addition, increased levels of LH (above 10 IU/L) indicate TD, even in the presence of normal total or free T levels. The presence of elevated LH indicates there is inadequate T-mediated negative feedback at the level of the hypothalamus and pituitary, which is a sign that the body needs higher T levels. Although this scenario has been considered a form of compensated subclinical hypogonadism, in the presence of symptoms, it should be considered clinical rather than subclinical and merits treatment. The new approach has also been acknowledged by the European Association of Urology (EAU) guidelines [10]. Evidence from the European Male Aging Study (EMAS) supports the concept that the combination of elevated LH levels and normal T may indicate TD [11].

I also use androgen receptor (AR) gene CAG repeat length in the assessment of men with possible TD, as a secondary step for men with symptoms of TD in association with normal T concentrations, or who fail to respond adequately to treatment. The CAG repeat length affects the sensitivity of the AR to circulating T concentrations. Some men with CAG repeat length >24 demonstrate symptoms of hypogonadism when T levels are within the lower normal range [12,13]. This approach is also now included in EAU guidelines [10].

Q: Published guidelines recommend obtaining two morning blood determinations for the diagnosis of TD, with treatment restricted to men in whom both results are below a threshold value. In your own practice, do you require two blood tests before offering TTh? Must the blood tests be obtained in the morning? Will you offer treatment to a man if one blood test is low and the other is within the normal range in a symptomatic man?

Khera: I typically obtain two T levels in men before starting TTh. In men above the age of 50, I am not as strict in obtaining a morning T as studies have demonstrated that men lose diurnal variation between roughly 40 to 50 years of age. However, if a younger man presents to my clinic in the afternoon, I would still consider checking his T level but would take into account that his T level would have been higher had I checked it in the morning. I would offer a symptomatic patient TTh if one T result was low and a second was in the low normal range. If there were a wide discrepancy between the two results (i.e., > 200 ng/dL), I may consider getting a third serum T with the suspicion that one of the results was due to lab error.

Maggi: I usually require a confirmation test for total T obtained in the morning. In the case of discordant results between the two tests, I use calculated free T to make the decision.

Zitzmann: Usually, we perform two blood tests and prefer to have them done during the morning hours. This is not a *conditio sine qua non*. If symptoms and results are clear, I would start T therapy after performing PSA and digital rectal exam (DRE)/transrectal ultrasound. Two tests are performed in cases with borderline levels of T/free T, together with LH levels and testicular ultrasound. A second step in ambiguous cases is determination of AR gene CAG repeat length. Note that CAG repeat length greater than 37 is rare and is associated with Kennedy's disease, a neurological disorder. However, CAG repeat length greater than 24 is seen in 10–15% of men depending on ethnicity and is associated with reduced response to circulating T concentrations [14]. Some men come for blood tests in the afternoon. Although this is not preferred, a low level will prompt a second test during morning hours. In hypogonadal men, the hypothalamic–pituitary–gonadal (HPG) axis is disturbed anyway, and this is why afternoon levels can indicate hypogonadism.

Q: Under what circumstances do you obtain additional tests of androgen status, such as free or bioavailable T? Which of those tests do you prefer? Do you use the free T index (total T concentration divided by SHBG concentration)? What threshold values do you use for these tests to help determine if a man has TD?

Khera: I obtain a calculated free T in almost all patients, as I believe free T is the best indicator of T status in a man. It is my impression that the calculated free T is more accurate than the direct free T assay. Some men will have normal total T levels due to significantly elevated SHBG levels, yet low levels of free T. Those patients at greatest risk for elevated SHBG levels include those who have liver disease, hyperthyroidism, human immunodeficiency virus, and elderly men, as SHBG increases with age. In fact, aging is associated with a greater increase in SHBG levels than it is a decline in total T levels [15]. This explains why free T declines more rapidly than total T with aging.

I do not use the free T index or bioavailable T.

Maggi: In my clinical practice, I routinely use calculated free T by the Vermeulen equation [16].

I use a threshold of 225 pmol/L, as suggested by several guidelines and the EMAS study [17].

Zitzmann: I always obtain testicular ultrasound at the first visit. Testes with a volume of less than 10 mL indicate disturbance of the HPG axis. This is another useful clue to the diagnosis of TD and can be used in decision making whether to begin TTh, or in male infertility cases with low levels of gonadotropins, for alternative treatments such as gonadotropins, tamoxifen, or clomiphene citrate. Especially the latter two are empirical, but can be helpful in my experience. When these various piece of the puzzle do not seem to fit, I also obtain dhydrotestosterone (DHT) levels by radioimmunoassay (RIA) and consider treatment for levels less than 300 pmol/L. Finally, I obtain thyroid tests—thyroid-stimulating hormone, free T4, and free T3, as well as thyroid ultrasound—as symptoms of hypothyroidism may resemble those of TD. Testing for DHT is diagnostic, and DHT supplementation is not a treatment in these men.

I routinely order free T and use the calculated free T according to the method of Vermeulen. I do not use the free androgen index.

Q: Do you use age-adjusted values for determination of TD?

Khera: No. Although I do consider comorbidities during my assessment, I do not find age-adjusted values to be helpful.

Maggi: I do not use age-adjusted threshold for starting T therapy. However, I do take into consideration that T secretion and metabolic clearance rates are physiologically decreased in older men, and therefore, the dose of T therapy should be lower than the production rate (5 mg per day), calculated in young individuals, (easily applicable to T transdermal preparations).

Zitzmann: No. As the EMAS study has revealed, T levels of young men are maintained up to old age (>80 years) when no comorbidities or obesity occur. The age adjustment that some labs offer is based on the inclusion of older men with comorbidities and/or obesity. These labs were not careful in selecting their reference cohorts. I do not believe age adjustment for T levels is necessary or useful.

Q: What other blood tests do you routinely obtain during the assessment of a man with symptoms suggestive of TD (e.g., LH, FSH, prolactin, etc.)? When do you measure SHBG and why?

Khera: Before initiating TTh, I test for serum total T, hematocrit, PSA, LH, FSH, and prolactin. I also obtain an SHBG in all patients to assess their calculated free T.

Finally, I perform a digital rectal exam on patients before initiating TTh.

Maggi: We recently proposed that PSA could represent a marker of T bioactivity [18]. In that study, the relationship between circulating T and PSA was described by an exponential curve with a sharp rise in the hypogonadal range and a flat plateau in the eugonadal one, according to the previously formulated "saturation hypothesis" of the biological effect of T [16]. After adjusting for age, low PSA was associated with hypogonadism-related features (i.e., delayed puberty, lower testis volume [TV], gynecomastia) and associated conditions, such as MetS and CV disease. Furthermore, low PSA was associated with impaired sex- and sleep-related erections and frequency of intercourse. Hence, a low PSA could help in identifying a low T state. The optimal threshold for detecting TT <8 nmol/L was at PSA <0.65 ng/mL.

I routinely measure LH and FSH, as these results may guide intervention and further testing. In men with low or inappropriately normal gonadotropins in association with low T values, I obtain pituitary magnetic resonance imaging and will test for other pituitary hormones. High LH indicates testicular dysfunction. A karyotype may be indicated in appropriate individuals. I also obtain SHBG in all men, as levels are unpredictable, perhaps because of genetic variation, and results are not predicted by other tests.

Zitzmann: I always obtain FSH together with LH, as I want to know about fertility status and testicular capacity. Prolactin is helpful to detect cases of secondary hypogonadism, as high prolactin levels indicate pituitary malfunction and also directly decrease Leydig cell function. I also often do tests of the other hormonal axes. Usually, this is performed at the first visit, because many patients come from places far away.

Q: Do findings on physical examination, such as small testicles, influence your decision making regarding the diagnosis of TD?

Khera: Small testicular size helps with making the diagnosis of hypogonadism. Attempts to raise endogenous T with clomiphene citrate or human chorionic gonadotropin are usually not successful when this finding is present together with elevated LH and FSH. Very small testicular volumes (<5 cc) leads me to order karyotype for possible Klinefelter's disease. In patients with small testicles, I inquire about testis trauma, exposure to

chemotherapy or radiation, and prior testis surgery. All of these can result in primary hypogonadism. I also check serum estradiol in men with gynecomastia. I also calculate body mass index (BMI) as men with obesity are more likely to have TD, and TTh has been shown to improve these conditions.

Maggi: Small age-adjusted prostate volume is, in my experience, a useful indicator of TD. I also measure TV by Prader orchidometer in every patient. Higher TV is positively associated with T and gonadotropin levels and also with overweight/obesity, smoking, alcohol abuse, and hypertension [19]. In the presence of a low T, a high TV suggests the presence of comorbidities, which must be screened, while a low TV indicates a possible impairment in sperm production, which should be confirmed by sperm count if the subject is interested in fertility. A very low TV (3–5 mL) with elevated gonadotropins is indicative of Klinefelter's syndrome and should be confirmed by karyotype.

Zitzmann: Yes. As previously mentioned, testicular volume <10 mL is indicative of disruption of the HPG axis.

Q: How do you monitor men treated with T? What do you check on physical examination, and what blood tests do you obtain? How often do you check those tests and see the patient after initiating treatment?

Khera: I initially ask my patients to return in 4–6 weeks to recheck their serum T levels. Although it may take up to 3 months for patients to experience symptomatic improvement, I would like to find out early if the patient is in the therapeutic T range and, if not, to adjust TTh accordingly. I then have patients return for follow-up every 4 months during the first year and every 6 months thereafter. If the patient is treated with subcutaneous T pellets, I will see him every 4 months for pellet insertion.

At each visit, I check serum total and free T levels, as well as hematocrit and PSA. After the first year, I order PSA less frequently. I see my patients on T therapy at least twice per year to monitor T, hematocrit, and PSA blood levels. I perform a DRE on these patients once per year as well. I periodically assess for gynecomastia and testicular atrophy.

Maggi: I monitor T administration by measuring hematocrit/hemoglobin and PSA, two independent markers of T bioactivity.

A hematocrit >54% is an indication to stop TTh until it decreases to a safer level, but phlebotomy can also be considered in the most severe cases. I monitor patients every 6 months during the first year of treatment and annually thereafter.

The goal of treatment is to replace normal T production, i.e., 5 mg/day. Although guidelines indicate treatment should maintain serum T levels within the physiological range, I personally adjust T dose more on the basis of hematocrit (making sure it does not go too high) and PSA (aiming not too low or too high) than on T levels itself. For long-acting injectable T preparations (T undecanoate), I measure T the day before the next injection. For men on transdermal gels, I obtain a blood test at least 2 hours after application.

Zitzmann: I monitor patients every 3 months in the first year. The major changes in hematocrit and PSA occur within the first few months. Prostate size is evaluated annually. Bone density is measured by dual X-ray absorptiometry as well as body composition, but not always. Semen parameters are routinely obtained, not only in men desiring paternity but also to assess testicular function and to exclude lower urinary tract infections in patients with complaints such as ED. I also monitor men with lipid profiles, fasting glucose, waist circumference, and BMI. I use questionnaires (Aging Male Symptom Questionnaire, International Index of Erectile Function, International Prostate Symptom Score) to assess outcomes. This is done for scientific reasons but is also useful in modifying the treatment with regard to dose or form of therapy.

Q: Will you treat a man who is symptomatic but has normal serum T? Is there a total T concentration above which you will NOT treat, regardless of symptoms?

Khera: If a symptomatic patient has low levels of free T, I will treat him even if his total T is normal, especially if SHBG is high, because this may mask the presence of low levels of free T. I also will consider treatment in a man with normal total T if his AR CAG repeats are high, because this is associated with insensitive ARs and these men require higher serum T concentrations to achieve symptomatic improvement.

If the patient has a normal total T, free T, and CAG repeat values, I would be reluctant to offer T therapy, particularly if total T is greater than 400 ng/dL and calculated free T is greater than 10 ng/dL (280 pmol/L).

Maggi: No, I will not treat a man that is symptomatic but has normal level of T because there is no evidence this is beneficial.

Zitzmann: Yes. I treat men with normal T when they have symptoms, and especially when CAG repeats are long, LH is elevated, DHT is low, or testes are small. None of these is diagnostic by itself, but is part of the overall assessment, and in particular I recognize there is no consensus regarding DHT concentrations in postpubertal men. For me, symptoms are the key. The man comes to see me with a problem, he is seeking my advice and help, and he deserves at least a trial of treatment if his clinical presentation is suggestive of TD. In uncertain cases, it can be beneficial to offer a trial of therapy for 3–6 months and then reassess.

Q: Will you treat a man with low T who is not symptomatic?

Khera: Men with low levels of T and signs of MetS should be considered for T therapy even if they have no symptoms, as there are emerging data to suggest this population benefits from T therapy. TTh has been shown to improve insulin resistance and reverse MetS. However, not all men with MetS have TD or symptoms of hypogonadism.

Maggi: I have never seen a man with low T without any symptom or sign of its deficiency. In fact, the spectrum of associated symptoms and signs is so wide that it is difficult, almost impossible, to find an individual without at least one of them.

Zitzmann: These men usually do not come to the clinic because they do not have symptoms. Occasionally, we detect low T incidentally in men who desire paternity. If the sperm count is low, we often treat with gonadotropins, tamoxifen, or clomiphene. Otherwise I would not treat.

Occasionally, men present with gynecomastia and reduced body hair. They may not report the classical symptoms of hypogonadism, such as loss of libido and lack of energy. This is likely because they have been hypogonadal for a long time, maybe their whole life, having barely or partially passed puberty. They do not know what a normal libido is. Usually, these men have very low T levels, below 4 nmol/L (120 ng/dL), and secondary hypogonadism. These men usually have decreased bone density, and we always treat them with T therapy.

If an asymptomatic man is found incidentally to have low T, but has normal testes, normal LH, and short AR gene CAG repeats, I would not treat but would recommend follow-up in 6–12 months, as T levels may drop further and they may become symptomatic.

Q: Recently, new concerns have been raised regarding CV risks with TTh based on two studies, one by Vigen et al. published in the *Journal of the American Medical Association* [20] and the other by Finkle et al. published in *Plos One* [21]. How have these studies influenced your practice? How do you counsel your patients regarding CV risk?

Khera: I have received many e-mails and phone calls from patients concerned about the results of these studies, and I feel it is important to acknowledge them with my patients. Both of these studies were poorly designed. Neither was randomized or placebo controlled, and the study by Finkle et al. did not have a control group. Therefore, it is not possible to tell whether these men had a CV event due to their underlying condition of TD or due to T usage. The former is more likely based on the literature. I am extremely concerned that these poorly designed articles will lead many patients to believe that T causes heart attacks. I tell my patients there are far more well-designed studies demonstrating that low T increases the risk for a heart attack and TTh decreases CV risk factors.

Maggi: These new studies have not substantially influenced my practice because I already discussed CV issues with my patients and colleagues. After careful review and analysis of these articles, these articles do not provide any believable evidence that TTh increases CV risk, because of the retrospective nature and the numerous flaws in their design. I was more impressed by the meta-analysis of randomized controlled trial (RCT) studies released by Xu et al. last year [22], showing an increased number of CV events in the T arm. However, together with Dr. Giovanni Corona, I have meta-analyzed again all published RCT studies and found no evidence for a deleterious effect of T on CV health. In addition, we detected even a protective effect of T on major adverse CV events, in particular in RCT studies involving subjects with metabolic diseases. This manuscript is in preparation. After 20 years of researching TTh, I strongly believe that T does not affect CV risk, and this is what I advise my patients.

Zitzmann: The publicity regarding the recently published studies about a possible CV risk during T substitution has made it important to discuss this issue with my patients, albeit few of my patients have asked about these articles. My review of these two new studies does not support new concerns regarding CV risk but makes me aware that patients should only be treated when their history is known, when T levels and other parameters have been assessed,

and when compliance management is effective. Generally speaking, this is a prerequisite in medicine anyhow, but it was obviously not the case in many of the patients whose data were used in these retrospective analyses. My greatest concern with the study by Vigen et al. is that most of these patients may actually not have been continuously treated by T replacement; they just received a prescription and were not followed. In addition, I was surprised by the attention received for the study by Finkle et al. because this study also refers to prescriptions and not case management. These reports are contradicted by previous literature that have shown CV benefits of T therapy, including two studies demonstrating reduced mortality in men with low T levels who received TTh compared with men who did not [23,24]. Those studies consisted of thorough approaches involving proper diagnostic procedures, measurement of T levels, and continuous follow-up of patients.

Nevertheless, I counsel my patients and also investigate their CV profile. ED can be a hint for CV risk. High hematocrit should be avoided and I am very careful regarding T substitution in men with a clinical picture of cardiac insufficiency of a higher grade (New York Heart Association classes 3 and 4).

Discussion and Summary

Morgentaler: In this article, an international panel of experts present their individual approaches to the challenging problem of identifying who is a candidate for T therapy. To the detailed description of their practices, I add here a brief summary of my own. In my practice, symptoms are paramount, with blood tests used to confirm the diagnosis in all cases. I obtain total and free T in all cases, together with hematocrit, LH, FSH, SHBG, estradiol, and prolactin. I find free T more useful than total T as a diagnostic test; however, it is critical to note that reference values provided by laboratories are not clinically based and of little value. Free T concentrations less than 100 pg/mL or RIA concentrations less than 1.5 ng/dL are consistent with TD. Although I use a total T value of less than 350 ng/dL (12 nmol/L) as indicative of TD, if the free T value is low, I consider the total T concentration irrelevant. Men routinely have more than one blood test obtained by time of treatment, but this is not a requirement, and I will offer treatment to a symptomatic man with characteristic symptoms and a single blood test result confirming the diagnosis. I do not require morning blood tests in men over 45 years, but will do so for younger men.

Although the experts described fairly similar general approaches, each describes one or more items they find particularly useful or important that is not shared by the others. Dr. Khera emphasized free T values and has a higher acceptable total T threshold than the others. Dr. Maggi values the ANDROTEST questionnaire he developed, and his evaluation emphasizes metabolic issues. Dr. Zitzmann finds value in LH results and he takes note of CAG repeats, which influence the sensitivity of the AR. It is notable that all of the experts seem to allow for individual variation in the presentation of TD, and Drs. Khera and Zitzmann in particular will offer a trial of treatment to symptomatic men with normal T concentration, presumably in the belief that symptoms may reflect a biological TD that is not manifested in serum T concentrations.

Symptoms were of key importance to all the experts. This is an important and relatively recent shift in the diagnosis and management of men with TD. There was no consensus on what total T concentration is indicative of TD. Drs. Maggi and Zitzmann echo two sets of international guidelines [2,3], whereas Dr. Khera uses a threshold of 400 ng/dL (13.5 nmol/L). However, Drs. Khera and Zitzmann are not rigid about this upper limit, as both stated they would offer treatment to a symptomatic man with levels above their "normal" threshold depending on additional factors, such as CAG repeats or free T levels.

Morning blood testing was preferred by the experts, but not mandatory for all of them, particularly if symptoms are strongly present and an afternoon blood test result reveals an unequivocally low T value. All experts use calculated free T to aid in the diagnosis. None use age-adjusted reference values. On physical examination, small testicular volume was considered a strong supportive sign for the diagnosis of TD. Dr. Maggi also finds the presence of a small prostate a helpful clue to the diagnosis.

Monitoring was an area with considerable individual variation among the experts. Dr. Khera has patients return at 4–6 weeks, and then at 4-month intervals in the first year, and every 6 months thereafter. Dr. Zitzmann has the patient return every 3 months in the first year and every 6 months thereafter. All experts monitor patients with hematocrit or hemoglobin as well as PSA. T levels are monitored by Drs. Khera and Zitzmann, but Dr. Maggi prefers to use PSA and hematocrit as biomarkers of

T activity. Dr. Zitzmann also obtains follow-up semen analyses to monitor testicular function and metabolic markers.

None of the experts found the new data suggesting increased CV risks with TTh to be compelling, and all noted there is substantial evidence to the contrary, namely that T therapy offers CV benefits. The highly statistical report by Vigen et al. [20] produced results that were contradicted by actual events, with the percentage of men who suffered an adverse event being lower by half in men who received T therapy compared with men who did not (10.1% vs. 21.2%). A published correction revealing major data shifts and contamination undermines this study further [25]. The study by Finkle et al. reported an increased rate of nonfatal myocardial infarction (MI) in a very short (up to 90 days) period after receiving a T prescription compared with the 12 prior months [21]. Because MI rates increase with age and because there was no control group of untreated men, this study is unable to offer any information as to whether T prescriptions are associated with increased, decreased, or unchanged rates of nonfatal MI.

In summary, these expert practices generally follow the main concepts of published guidelines, with some important departures. What impressed me most in learning how these experienced clinicians and researchers approached the problem of identifying men who are candidates for T therapy is their dedication to "getting it right." Each recognizes the importance that T therapy can have for a man's health and quality of life. Given the wide range of effects T exerts on the body, clinicians must be cognizant that the manifestations of TD can vary considerably, and atypical presentations are not rare. The lesson is that a humanistic approach requires considering the individual as a whole rather than as a simple blood test result, and that in equivocal cases, there may be value in an empirical trial of therapy.

Corresponding Author: Abraham Morgentaler, MD, Men's Health Boston, One Brookline Place, Suite #624, Brookline, MA 02467, USA. Tel: 617-277-5000; Fax: 617-277-5444; E-mail: dr.morgentaler@menshealthboston.com

Conflict of Interest: Dr Morgentaler discloses he has received research grants from Eli Lilly and Co, and Auxilium, has received payment for work as a consultant or for serving on the scientific advisory boards for AbbVie and Auxilium, and honoraria from Bayer and Merck.

Statement of Authorship

Category 1

(a) Conception and Design
Abraham Morgentaler; Mohit Khera; Michael Zitzmann; Mario Maggi

(b) Acquisition of Data
Abraham Morgentaler; Mohit Khera; Michael Zitzmann; Mario Maggi

(c) Analysis and Interpretation of Data
Abraham Morgentaler; Mohit Khera; Michael Zitzmann; Mario Maggi

Category 2

(a) Drafting the Article
Abraham Morgentaler; Mohit Khera; Michael Zitzmann; Mario Maggi

(b) Revising It for Intellectual Content
Abraham Morgentaler; Mohit Khera; Michael Zitzmann; Mario Maggi

Category 3

(a) Final Approval of the Completed Article
Abraham Morgentaler; Mohit Khera; Michael Zitzmann; Mario Maggi

References

1 Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95:2536–59.
2 Wang C, Nieschlag E, Swerdloff R, et al. Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. Eur Urol 2009;55:121–30.
3 Buvat J, Maggi M, Gooren L, Guay AT, Kaufman J, Morgentaler A, Schulman C, Tan HM, Torres LO, Yassin A, Zitzmann M. Endocrine aspects of male sexual dysfunctions. J Sex Med 2010;7:1627–56.
4 Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM. Testosterone therapy in adult men with androgen deficiency syndromes: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2006;91:1995–2010.
5 Powers JH. Practice guidelines: Belief, criticism, and probability. Arch Intern Med 2011;171:15–7.
6 Lazarou S, Reyes-Vallejo L, Morgentaler A. Wide variability in laboratory reference values for serum testosterone. J Sex Med 2006;3:1085–9.
7 Corona G, Rastrelli G, Vignozzi L, Mannucci E, Maggi M. How to recognize late-onset hypogonadism in men with sexual dysfunction. Asian J Androl 2012;14:251–9.
8 Corona G, Rastrelli G, Maggi M. Diagnosis and treatment of late-onset hypogonadism: Systematic review and meta-analysis of TRT outcomes. Best Pract Res Clin Endocrinol Metab 2013;27:557–79.
9 Rastrelli G, Corona G, Vignozzi L, Maseroli E, Silverii A, Monami M, Mannucci E, Forti G, Maggi M. Serum PSA as a predictor of testosterone deficiency. J Sex Med 2013;10:2518–28.

10 EAU Guidelines. Available at: http://www.uroweb.org/gls/pdf/17_Male_Hypogonadism_LR.pdf (accessed December 2, 2013).
11 Tajar A, McBeth J, Lee DM, Macfarlane GJ, Huhtaniemi IT, Finn JD, Bartfai G, Boonen S, Casanueva FF, Forti G, Giwercman A, Han TS, Kula K, Labrie F, Lean ME, Pendleton N, Punab M, Silman AJ, Vanderschueren D, O'Neill TW, Wu FC. European Male Aging Study Group. Elevated levels of gonadotrophins but not sex steroids are associated with musculoskeletal pain in middle-aged and older European men. Pain 2011 Jul;152:1495–501.
12 Schneider G, Nienhaus K, Gromoll J, Heuft G, Nieschlag E, Zitzmann M. Aging males' symptoms in relation to the genetically determined androgen receptor CAG polymorphism, sex hormone levels and sample membership. Psychoneuroendocrinology 2010 May;35:578–87.
13 Francomano D, Greco EA, Lenzi A, Aversa A. CAG repeat testing of androgen receptor polymorphism: Is this necessary for the best clinical management of hypogonadism? J Sex Med 2013 Oct;10:2373–81.
14 Liu CC, Lee YC, Wang CJ, Yeh HC, Li WM, Wu WJ, Huang CN, Bao BY, Huang CH, Huang SP. The impact of androgen receptor CAG repeat polymorphism on andropausal symptoms in different serum testosterone levels. J Sex Med 2012 Sep;9:2429–37.
15 Wu FC, Tajar A, Beynon JM, et al. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med 2010;363:123–35.
16 Vermeulen A. Hormonal cut-offs of partial androgen deficiency: A survey of androgen assays. J Endocrinol Invest 2005;28(3 suppl):28–31.
17 Huhtaniemi IT, Tajar A, Lee DM, O'Neill TW, Finn JD, Bartfai G, Boonen S, Casanueva FF, Giwercman A, Han TS, Kula K, Labrie F, Lean ME, Pendleton N, Punab M, Silman AJ, Vanderschueren D, Forti G, Wu FC, Group EMAS. Comparison of serum testosterone and estradiol measurements in 3174 European men using platform immunoassay and mass spectrometry; relevance for the diagnostics in aging men. Eur J Endocrinol 2012;166:983–91.
18 Morgentaler A. Testosterone replacement therapy and prostate cancer. Urol Clin North Am 2007;34:555–63.
19 Rastrelli G, Corona G, Lotti F, Boddi V, Mannucci E, Maggi M. Relationship of testis size and LH levels with incidence of major adverse cardiovascular events in older men with sexual dysfunction. J Sex Med 2013;10:2761–73.
20 Vigen R, O'Donnell CI, Baron AE, et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013;310:1829–36.
21 Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, Fraumeni JF Jr, Hoover RN. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS ONE 2014 Jan 29;9:e85805. doi: 10.1371/journal.pone.0085805.
22 Xu L, Freeman G, Cowling BJ, Schooling CM. Testosterone therapy and cardiovascular events among men: A systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med 2013;11:108.
23 Muraleedharan V, Marsh H, Kapoor D, Channer KS, Jones TH. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol 2013;169:725–33.
24 Shores MM, Smith NL, Forsberg CW, Anawalt BD, Matsumoto AM. Testosterone treatment and mortality in men with low testosterone levels. J Clin Endocrinol Metab 2012;97:2050–8.
25 Incorrect number of excluded patients reported in the text and figure. JAMA 2014;311:967.