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EXAMINING THE ISSUES, TREATMENTS, AND EMERGING TRENDS IN DIABETES & ENDOCRINE DISORDERS
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The Management of Low Testosterone

Current Approaches, New Possibilities

A ROUNDTABLE DISCUSSION WITH

- ANDRE T. GUAY, MD
- MOHIT KHERA, MD, MPH, MBA
- DENIS I. BECKER, MD
- BARRY HOROWITZ, MD
- PHILIP J. MIKA, MD
- STEPHEN J. WINTERS, MD

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STATEMENT OF NEED

Hypogonadism is one of the main causes of male infertility. It is estimated that 13 million men in the United States alone are affected by hypogonadism, yet less than 10% of these men actually seek treatment for the disorder. Hypogonadism occurs when there is disease or damage to the pituitary gland, testicles, or hypothalamus. Any problems in these areas can lead to a deficient production of the gonadotropin hormone.

Hypogonadism prevalence increases with age, and it is generally underdiagnosed and undertreated. Symptoms of low testosterone are often subtle and nonspecific. Not only has the definition of low testosterone been debated for years, but to further complicate matters, the measurement of testosterone levels has not been standardized, and a particular assay may be inaccurate.

Few large, randomized clinical trials adequately address prostate safety during long-term testosterone therapy. Low testosterone has been associated with diabetes, insulin resistance, metabolic syndrome, and other comorbidities. Despite these controversies and the paucity of conclusive evidence, physicians must still address hypogonadism in their practices.

Men with low testosterone were more likely to have elevated markers of inflammation—inflammatory cytokines—which contribute to many diseases. Another characteristic that distinguished the men with low testosterone was a larger waist girth along with a cluster of cardiovascular and diabetes risk factors related to this type of fat accumulation.

TARGET AUDIENCE

This activity is designed for endocrinologists, internists, and primary care physicians, as well as other specialists involved in the treatment of patients with endocrine disease.

LEARNING OBJECTIVES

Upon successfully completing this learning program, participants should be able to:

- Recognize that hypogonadism is prevalent and undertreated.
- Understand the different definitions of hypogonadism and their clinical application.
- Detail the issues regarding the measurement of testosterone levels.
- Evaluate the evidence relating testosterone therapy and prostate health.
- Review the safety and compliance issues related to therapy options.
- Describe the association of diabetes, insulin resistance, metabolic syndrome, and other comorbidities with low testosterone levels.
- Review the advantages of available treatment options.
- Better understand the patient benefits associated with each of the therapy options.
- Apply current guidelines for the treatment of hypogonadism.

METHOD OF INSTRUCTION

Participants should read the learning objectives and continuing medical education (CME) program in their entirety. After reviewing the material, they must complete the self-assessment test, which consists of a series of multiple-choice questions. To answer these questions online and receive real-time results, please visit www.dulaneyfoundation.org and click "Online Courses."

If you are experiencing problems with the online test, please e-mail us at support@dulaneyfoundation.org and explain the details of any problems you encounter with the Web site. Alternatively, you can fax your exam to us at +1 610 771 4443. Please note, in order to receive your certificate and credit when faxing your test, you must include your full name as well as an e-mail address, as certificates will be issued electronically. Upon completing the activity and achieving a passing score of over 70% on the self-assessment test, you may print out a CME credit letter awarding *1 AMA/PRA Category 1 Credits.*™ The estimated time to complete this activity is 1 hour.

ACCREDITATION

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of The Dulaney Foundation and *Review of Endocrinology*. The Dulaney Foundation designates this educational activity for a maximum of *1 AMA/PRA Category 1 Credits.*™ Physicians should only claim credit commensurate with the extent of their participation in the activity.

DISCLOSURE

In accordance with the disclosure policies of The Dulaney Foundation and to conform with ACCME and FDA guidelines, all program faculty are required to disclose to the activity's participants: (1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices or providers of commercial services; and (2) the identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

FACULTY CREDENTIALS

Andre T. Guay, MD, is Clinical Assistant Professor of Medicine (Endocrinology) at Harvard Medical School, and Director, Center For Sexual Function/Endocrinology, Lahey Clinic Northshore, Peabody, Mass.

Mohit Khera, MD, MPH, MBA, is Assistant Professor of Urology, Scott Department of Urology Baylor College of Medicine, Waco, Texas.

Denis I. Becker, MD, is Associate Consulting Professor, Endocrinology, Metabolism & Nutrition at Duke University, Durham, NC, and he is also in private practice at Raleigh Endocrine Associates, Raleigh, NC.

Barry Horowitz, MD, is with Palm Beach Diabetes and Endocrine Specialists and is Co-Director, Metabolic Research InstituteWest Palm Beach, Fla.

Philip J. Mika, MD, is with CapitalCare Internal Medicine & Endocrinology and is Chief of Endocrinology, Ellis Hospital, in Schenectady, NY.

Stephen J. Winters, MD, is Professor of Medicine and Chief, Division of Endocrinology and Metabolism, at the University of Louisville, Lousiville, Ky.

FACULTY DISCLOSURE DECLARATIONS

Dr. Guay states that he is a paid investigator for Auxilium, Solvay, Indevus, and Bayer/Schering AG.

Dr. Khera states that he has received a research grant from Pfizer and that he is a paid consultant for Solvay and Vivus.

Dr. Becker states that he is a member of the speaker's bureau for Auxilium and Solvay, and has been a paid consultant for Auxilium.

Dr. Horowitz states that he has no financial relationships to disclose.

Dr. Mika states that he is a paid consultant for Sanofi-Aventis, GlaxoSmithKline, Novartis, Novo Nordisk, Takeda, Pfizer, and Astra Zeneca.

Dr. Winters states that he is a paid consultant for Auxilium and ProStrakan Pharmaceuticals.

Additional staff who assisted with preparing this supplement, Sharon Sjulstadt, RN, Alan Guralnick, Conni B. Koury, Erin Corr, and Amy Oravec, state that they have nothing to disclose.

CO-CHAIRS

Andre T. Guay, MD
Clinical Assistant Professor of Medicine (Endocrinology), Harvard Medical School, Director, Center For Sexual Function/ Endocrinology, Lahey Clinic Northshore, Peabody, Mass

Mohit Khera, MD, MPH, MBA
Assistant Professor of Urology, Scott Department of Urology
Baylor College of Medicine
Waco, Texas

PARTICIPANTS

Denis I. Becker, MD
Associate Consulting Professor, Endocrinology, Metabolism & Nutrition
Duke University, Durham, NC
Raleigh Endocrine Associates, Raleigh, NC

Philip J. Mika, MD
CapitalCare Internal Medicine & Endocrinology
Chief of Endocrinology, Ellis Hospital
Schenectady, NY

Barry Horowitz, MD
Palm Beach Diabetes and Endocrine Specialists
Co-Director, Metabolic Research Institute
West Palm Beach, Fla

Stephen J. Winters, MD
Professor of Medicine and Chief, Division of Endocrinology and Metabolism
University of Louisville
Louisville, Ky

Current Approaches, New Possibilities: The Management of Low Testosterone

Review of Endocrinology convened a roundtable of experts to discuss comprehensive patient-management strategies for monitoring and treating patients with low testosterone levels. The participants reviewed currently available treatment options and assessed the safety, tolerability, and efficacy of these options.

Andre T. Guay, MD: I am sure we all agree that hypogonadism is prevalent and undertreated, but why?

Denis I. Becker, MD: My strong bias as to why hypogonadism is undertreated is because many physicians are only interested in sexual dysfunction. If a patient is not complaining of sexual dysfunction, often physicians will not look for hypogonadism. I like to remind physicians that eugonadism promotes eumetabolism.

Barry Horowitz, MD: The analogy I draw is to osteoporosis. When I came out of my fellowship, there was very little available to treat osteoporosis, so endocrinologists received a lot of referrals from primary care physicians (PCPs). When Fosamax (alendronate sodium; Merck, Whitehouse Station, NJ) came on the market, PCPs started treating osteoporosis, and I often found a proper work up was not done. A similar situation is happening now. Once Viagra (sildenafil citrate; Pfizer, New York, NY) became available, sexual dysfunction got into the realm of the PCPs. In many cases, however, PCPs are ignoring the root cause. A work up does not get done because they are not looking for hypogonadism, and they are not asking the right questions.

Philip J. Mika, MD: I believe also that PCPs rely heavily on the normal values printed on laboratory sheets, and they get kind of a tunnel vision. There is a lack of recognition with regard to hypogonadism and a lack of awareness to even look for it.

Horowitz: There may also be some discomfort on the part of the physician in discussing the topic with their patients. I have a fairly typical endocrine practice in south Florida, and about 65% of my patients see me for diabetes management. When I ask about sexual function and libido, the look of relief that comes across many of their faces is palpable. A wise endocrinologist told me once, if you do not ask about it, they are not going to tell you.

Stephen Winters, MD: In my experience, general internists and PCPs are not always knowledgeable about testosterone deficiency or comfortable with its treatment.

Guay: A Harris poll[1] of 522 men aged >39 years revealed that 91% did not know one symptom of hypogonadism (see *Symptoms and Signs of Low Testosterone*). When they were told what the symptoms were, 95% of the men said their doctor never asked them about it. Would you also consider that another reason for undertreatment is unfamiliarity with the symptoms? Physicians do not know that low energy is the most common symptom of low testosterone, and they are also confused about testing for hypogonadism.

Horowitz: There is no easy fix with low-testosterone treatment. We have choices, but they are not the easiest of choices—between gels and patches—but it is not as simple as taking a pill. Also, many physicians do not know the ins and outs of potential

SYMPTOMS AND SIGNS OF LOW TESTOSTERONE

Testosterone is an important male hormone produced mainly in the testicles. It helps the body develop male characteristics during puberty and it also plays a central role in maintaining healthy sexual function and body composition in adult males. Low testosterone or hypogoandism affects as many as 13 million American men,* and occurs when the body is unable to produce sufficient quantities of testosterone. Hypogonadism can be caused by many factors, including certain genetic conditions, testicular damage or infection, and exposure to toxins, radiation, or chemotherapy.† Low testosterone is often associated with aging. The goal of testosterone replacement therapy is to return testosterone levels into the normal range and relieve symptoms.

Symptoms associated with low testosterone include:

- Increased body fat, body mass index
- Reduced muscle bulk and strength
- Low bone mineral density
- Loss of body hair (axillary and pubic),
- Reduced shaving

Signs associated with low testosterone include:

- Decreased energy or motivation
- Depressed mood
- Diminished libido, erectile dysfunction
- Poor concentration and memory
- Sleep disturbances

* Mulligan, *Int J Clin Pract.* 2006;60: 762-769.
† American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients–2002 update. *Endocr Pract.* 2002;8:439-456.

side effects and are unclear regarding how to monitor treatment.

Guay: There is also the issue of asympomatic versus symptomatic hypogonadism. Some men may have symptoms but have a testosterone level of 320 ng/dL, and they are ignored because their physician thinks they are normal. The MMAS (Massachusetts Male Aging Study[2]) is a great tool, but like any other longitudinal study, the questions thought of 20 years before are not necessarily the important questions of today.

Horowitz: I think in that study in particular, the prevalence of low testosterone is underreported because the definition they used is too restricted.

Mohit Khera, MD, MPH, MBA: How would you change it?

Horowitz: They used testosterone levels <200 ng/dL or 200 to 400 ng/dL with symptoms. I think you need to be a little broader in your definition in terms of symptoms and levels.

Winters: The Venn diagram in the recent MMAS is very telling. It shows that men with low hypogonadism symptom scores most often have normal testosterone levels. Symptoms of low testosterone are very nonspecific, so you really need to look at both the testosterone levels and symptoms.

Khera: You also have to question the cutoff they use of the IIEF (International Index of Erectile Function)—17—many would argue that 21 would be a limit. I believe even mild symptoms of erectile dysfunction are early signs of hypogonadism, and the MMAS authors used moderate symptoms in the study. The questionnaire they used to assess libido is too simple. It is a nonvalidated single question rating libido from 1 to 5.

Becker: Even a testosterone level of 150 or 200 ng/dL is two standard deviations below the mean, and if you wait until the level is that low to make a diagnosis of hypogonadism, you are going to miss the mildly hypogondal patients. A drop in testosterone to 150 ng/dL represents an increased risk of metabolic syndrome of 57%.[3]

Guay: The Endocrine Society's algorithm states that if the total testosterone level is under 300 ng/dL, a free testosterone level could be obtained (Figure 1).[4] A European algorithm developed by the European Urology Association, the International Andrology Society, and the International Society of Aging Men, is more realistic (Figure 2): If testosterone is <230 ng/dL, treat it (symptoms or not), and if it is >350 ng/dL, the patient is probably OK.[4] In the middle is unclear, so that is when you do your bioavailable or free testosterone, and then if you are still not sure, give a treatment trial.

Becker: The Endocrine Society and the American Association of Clinical Endocrinologists guidelines say start to treat when you get to a very low level and then treat up to 400 or 450 ng/dL. There is discordance between the willingness to start treatment and the goal of therapy—to get patients back to the mean.

Guay: That is because we do not have a good handle on thresholds. One good article on thresholds showed that when young castrate men were replaced very slowly, maximum nocturnal erections were achieved when testosterone levels were between 200 and 300 ng/dL, a level of >300 ng/dL did not increase erectile capacity at night.[5]

Becker: Sexual dysfunction is important symptom of low testosterone. But if you recognize that the myocardium is interested in healthy circulation and that you can improve a person's Bruce stage of exercise tolerance with 1 month of testosterone, then maybe repletion is more important to the optimization of cardiac function than to just the enhancement of libido or potency.

Guay: Is everybody aware of the HIM (Hypogonadism in Males) Study? The authors found a 38% prevalence of hypogonadism in a sample of 95 practices among men aged ≥45 years. Of the patients who were being treated, 30% were undertreated, which tells us that many physicians do not know where to go with the treatment.

> "The HIM study investigators found a 38% prevalence of hypogonadism in a sample of 95 practices, among men aged ≥45 years."
>
> —Dr. Guay

Becker: The lack of compliance and continuity of replacement therapy is probably due to not achieving adequately effective blood levels of testosterone and not asking the patient to come back often enough.

Guay: I use clomiphene, off label, to raise testosterone levels in secondary hypogonadism when fertility is desired and there is a potentially correctable cause, such as obstructive sleep apnea (OSA), stress, or acute illness. We raised testosterone levels in 170 men to 400 to 500 ng/dL, and the endpoint was sexual function.[6]

THE ADAM QUESTIONNAIRE

The ADAM questionnaire* was developed by a physician and is used extensively by health care providers to help identify men who may have low testosterone.

1. Do you have a decrease in libido?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased "enjoyment of life?"
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noticed a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

A YES answer to questions 1 or 7 or any three other questions indicates that the patient may have low testosterone.

*Adapted from Morley JE, et al. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism.* 2000;49:1239–1242.

For many patients, sexual function is the most important endpoint, but treatment may help mood and energy and not erectile function. My study found that only 39% of patients were cured of their erectile function; regression analysis showed that those who did not get better had diabetes, hypertension, etc. Treatment is not a cure all, as testosterone is an underpinning for other things such as metabolic syndrome and circulation.

AT-RISK POPULATIONS AND SCREENING TOOLS

Khera: What are the current screening tools the panel uses to diagnose hypogonadism, and what populations should be screened?

Howowitz: I have a large population of diabetic patients, and in every new diabetic male, in the review of systems, I ask questions and often come up with hypogonadism. I have access to the androgen decline in the aging male (ADAM) questionnaire (see *The Adam Questionnaire*), but I do not use it.

Becker: I keep the questionnaire available in the wait-

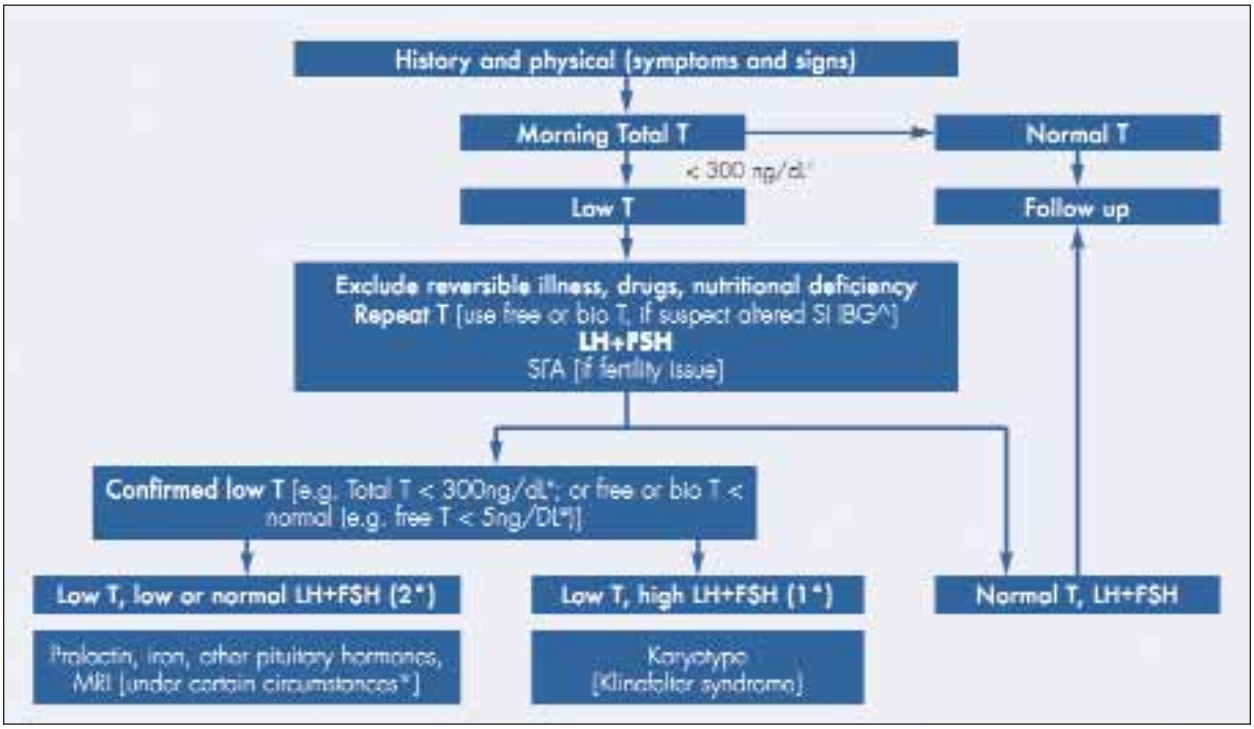

Figure and caption from the Endocrine Society's Clinical Guidelines, Testosterone Therapy in Adult Men with Androgen Deficiency Syndrome.

Figure 1. An approach for the diagnostic evaluation of adult men suspected of having androgen deficiency.
T = testosterone; bio T = bioavailable T; SFA = seminal fluid analysis; 1° = primary testicular failure; 2° = secondary hypogonadism. # = In some laboratories, the lower limit of the normal testosterone range in healthy young men is approximately 300 ng/dL (10.4 nmol/L); however, this range may vary in different laboratories. Use the lower limit of the range established in your reference laboratory. ^ = Refer to Table 1 for a list of conditions that alter SHBG concentrations. @ = In some reference laboratories, the lower limit of the normal free testosterone range in healthy young men is approximately 5 ng/dL (0.17 nmol/L) (approximate lower limit of normal in three major commercial laboratories) using equilibrium dialysis or calculated from total testosterone and SHBG; however, this range may vary in different laboratories (approximate lower limits of normal ranging from 4 to 9 ng/dL [0.14 to 0.31 nmol/L] in major commercial laboratories) using equilibrium dialysis or calculated from total testosterone and SHBG and the reference population used. Use the lower limit of the range established in your reference laboratory. * = Perform pituitary imaging (MRI) to exclude pituitary and/or hypothalamic tumor or infiltrative disease, if severe secondary hypogonadism (serum T <150 ng/dL), panhypopituitarism, persistent hyperprolactinemia, or symptoms or signs of tumor mass effect, such as headache, visual impairment, or visual field defect, are present.

ing room. One of the most important ICD-9 codes we use for screening for low testosterone is 780.79, fatigue.

Guay: ADAM'S specificity is 30% and International Society for the Study of the Aging Male's questionnaire has a specificity of 39%; that is why we need to develop a better one.

Horowitz: That is why I do not use it.

Guay: More specific questions to ask are about the power of ejaculation and seminal volume; even dry eye and sleeping disorders are affected by testosterone.

Winters: Although men with OSA are certainly an at-risk group for hypogonadism, there are reports that sleep apnea may worsen with testosterone therapy. In fact, some physicians view OSA as a contraindication to testosterone replacement.

Guay: There is one meta-analysis in diabetic patients showing that 30% to 40% have low testosterone. I have found that many men who have a variety of chronic illnesses will have a low testosterone level. In our *Aging Male* abstract, we found a 34% prevalence in diabetic men, 31% among those with hypertension, and 64% in men with OSA.[7] I diagnose OSA in my hypogonadal patients.

Winters: But men with OSA or type 2 diabetes are generally obese. In fact, a study at our institution showed that almost all of the relationship between low total testosterone and type 2 diabetes can be accounted for by obesity.

Guay: The data are amazing on obesity's relationship with low testosterone.

Becker: A five-point change in body mass index correlates to a 65% higher incidence of hypogonadism.[8]

Winters: Other at-risk groups for low testosterone, in addition to patients with diabetes, obesity, chronic obstructive pulmonary disease (COPD), and OSA, are those with chronic renal insufficiency, HIV, weight loss and other catabolic conditions, stress, and men treated with opiates or glucocorticoids.

Guay: What about the measurements? Total testosterone is our standard—it is inexpensive and available. Do you measure bioavailable or free testosterone? And if so, which free testosterone measurement?

> "In most cases, total testosterone is sufficiently sensitive and specific for the diagnosis of male hypogonadism."
>
> — Dr. Winters

Winters: In most cases, total testosterone is sufficiently sensitive and specific for the diagnosis of male hypogonadism.

In overweight men, sex hormone-binding globulin (SHBG) is generally low (Table 1). As a result, the total testosterone is low. On the other hand, SHBG levels are elevated in many older men and increase the total testosterone level. I think that additional assays are needed in these men. Analog-free testosterone assays are inaccurate and do not measure free testosterone. Instead, they measure a portion of the total testosterone, of approximately 0.6%. You can measure non-SHBG testosterone using ammonium sulfate precipitation, which includes the free and albumin-bound testosterone, giving you the bioavailable testosterone. Alternatively, you can calculate the free-testosterone level from the total testosterone and the level of SHBG, or you can measure the percent free testosterone by equilibrium dialysis. These approaches give very similar results. The problem is that these methods are not yet standardized, and age-adjusted normal results are lacking.

Khera: If a patient presented with a 330 ng/dL testosterone level and symptoms do you need the free testosterone test to treat?

Winters: The Endocrine Society practice guidelines say that this value is in the gray zone, because hypogonadism is defined as a total testosterone level of <300 ng/dL.[9] Because some people—particularly older men—have higher SHBG levels, total testosterone will be higher, and the free fraction will be lower. In older men, you are more likely to diagnose low testosterone using assays for free testosterone but are more likely to find a normal value in a young adult man who is overweight when total testosterone is at borderline levels, such as 330 ng/dL. I think that a measure of free testosterone is very helpful in that case.

Horowitz: If testosterone is borderline and the patient has symptoms and free or bioavailable testosterone measurement is still borderline, would you give him a therapeutic trial? I would.

Guay: The professional societies say you should give a trial.

Horowitz: Then one could say you could skip that step of measuring the free or bioavailable testosterone.

Guay: We have to account for age. A low-normal free testosterone level in a 30-year-old man is much more significant than in a 60-year-old man. When I use total testosterone in my men aged <50 years, I set my mental bar at 400 ng/dL, and if they are aged <40 years, I set it at 450 ng/dL. You have to adjust it in your mind based on your clinical experience with knowledge of how your laboratory works and what the normal values are for your population.

CLINICAL ISSUES WITH TESTOSTERONE TREATMENT

Becker: In the clinical arena, we have to be sensitive to the patient's clinical benefit. We will miss possibly an entire generation of therapy if we wait for long-term outcome studies that we do not yet have. By not treating a 65-year-old man with a testosterone level of 300 ng/dL, you may be condemning him to the greater

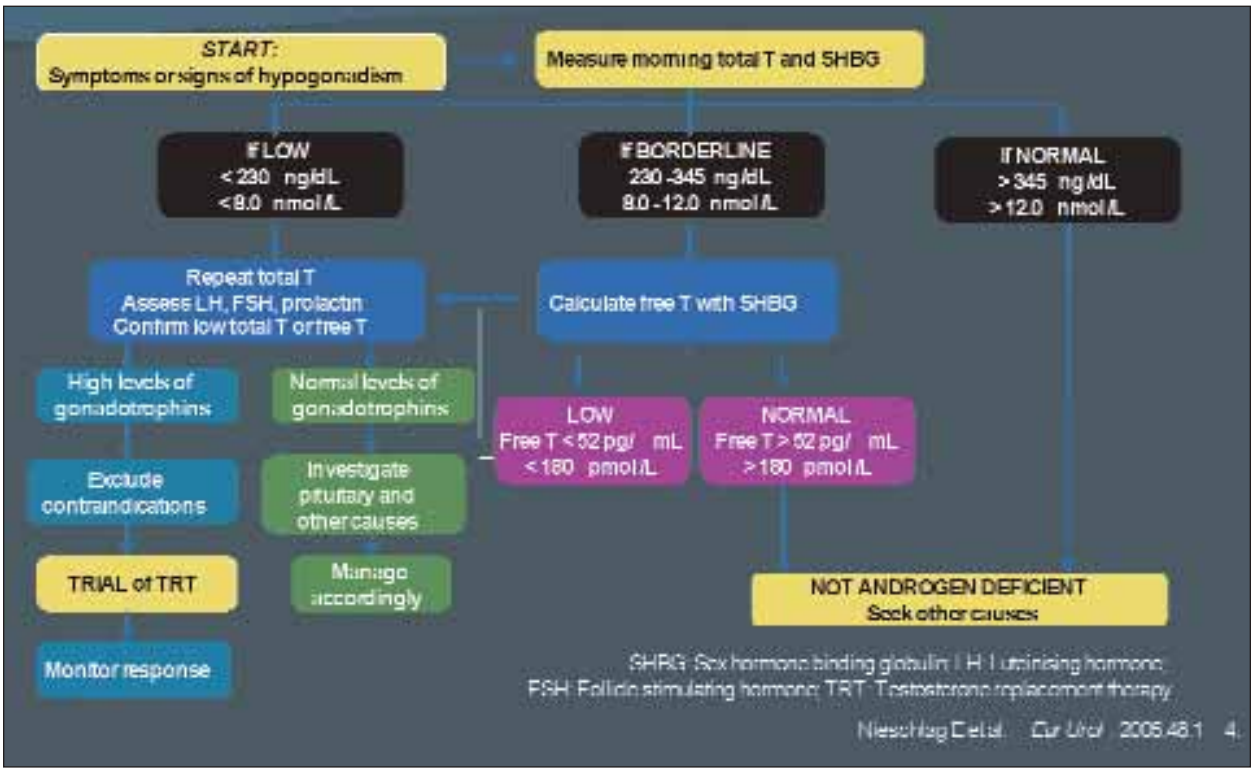

Figure 2. Diagnosis and treatment algorithm for low testosterone from the International Society of Andrology, the International Society for the Study of the Aging Male, and the European Association of Urology.

risks associated with the metabolic syndrome, including an earlier myocardial infarction (MI). I would be willing to treat that person. It has been demonstrated that 65-year-old men with prostate carcinoma, made hypogonadal with 6 months of androgen suppression therapy, have earlier fatal MIs.[10]

Guay: Low testosterone levels do not kill people, but it is associated with conditions, like metabolic syndrome and insulin resistance, that do have increased cardiovascular mortality risk. It is a marker. Pittleroud et al created insulin resistance, and the subsequent treatment with testosterone corrected the insulin resistance within 48 hours.[11]

Winters: There is an interesting and important bidirectional relationship between testosterone and adipose tissue, but to say that low testosterone causes heart disease and that replacing testosterone will improve heart disease risk seems premature.

Guay: Kapoor et al have data on reversing metabolic syndrome with testosterone therapy; levels of inflammatory cytokines go down as well.[12]

Winters: I read this interesting article and await confirmatory reports. Supraphysiological doses of testosterone suppress HDL cholesterol; the key to replacement therapy is keeping levels physiological.

Horowitz: How do we define a borderline level of testosterone? At what level of testosterone do you say this patient has symptoms, but the total testosterone level is normal, and I am not going to treat? This is a real-world situation.

Becker: In my real world, I have been uniformly disappointed with the usefulness of free testosterone assays in any sort of a clinical setting. I will always treat the patient based on total testosterone levels and clinical presentation.

Guay: At Lahey, we use the calculated free (the Sodergard equation). This uses total testosterone, SHBG, and the actual albumin level. I find that the free is very helpful. We see more articles being published using this technique, and it may be more useful than using equilibrium dialysis free testosterone, depending on the reliability of the reference laboratory.

EVALUATING THERAPY, PROSTATE HEALTH, AND SAFETY

Khera: How many of you treat postradical prostatectomy patients with testosterone?

Becker: We encourage tretment and have the patient discuss it with his urologist.

Khera: We recently presented data at the American Urological Association on 21 patients postradical prostatectomy treated with testosterone.[13] A review of the literature revealed only 18 other such patients. We now have >50 patients, and we have not had a recurrence of prostate-specific antigen (PSA) in this group. Now, I am conducting a randomized controlled clinical trial to look at the efficacy of testosterone starting 3 months postradical prostatectomy in patients with undetectable PSAs.

Potency rates are really important to urologists after radical prostatectomy. If you take potency away from a 40-year-old man, that is a problem. What is the role of testosterone in promoting erectile function and penile preservation? Our opinion is that testosterone is very important. The question is, if you have a patient who is hypogondal after radical prostatectomy and you are unwilling to raise his testosterone level to make him eugonadal, then you should consider making your eugonadal patients hypogonadal. Either it is safe or it is not.

Winters: According to the *Physician's Desk Reference*, prostate cancer is a contraindication to testosterone therapy. Until careful, long-term studies show otherwise, I am hesitant to prescribe androgens for these men, but this is an important issue.

Khera: The question is the effect of testosterone on the prostate itself. We know that testosterone increases PSA level, but most of the literature will support that it does not raise it significantly. We will use Testim (1% testeroneone gel; Auxilium Pharmaceuticals, Inc., Malvern, PA) in the study I mentioned previously.

Marks et al[14] showed the effect of serum testosterone on prostatic tissue levels. He treated 44 men with testosterone for 6 months and performed a biopsy before and after treatment. He found that all serum testosterone levels significantly increased, but there was no change in prostatic testosterone levels.

Becker: Whenever I have a patient that I am treating with replacement therapy, I watch the PSA level. If it rises, I ask the patient to stop therapy and to see his urologist to undergo a biopsy. This most often comes back negative. Will that patient have to repeatedly go through this cycle?

TABLE 1. CONDITIONS ASSOCIATED WITH ALTERATIONS IN SHBG CONCENTRATIONS

Conditions associated with decreased SHBG concentrations:
- Moderate obesity*
- Nephrotic syndrome*
- Hypothyroidism
- Use of glucocorticoids, progestins, and androgenic steroids*

Conditions associated with increased SHBG concentrations:
- Aging*
- Hepatic cirrhosis*
- Hyperthyroidism
- Use of anticonvulsants*
- Use of estrogens
- HIV infection

*Particularly common conditions associated with alterations in SHBG concentrations.

Source: Endocrine Society Guidelines

Khera: Yes. If you see a rise, you cannot take a chance—velocity is the key. Smaller prostates have larger rises in PSA, because they are returning to their normal level. A larger prostate has smaller rises in PSA, and recent data show us that an average rise in PSA of men on testosterone replacement therapy is anywhere from 0.46 to 1 ng/dL, so a greater rise is of concern.

Horowitz: I only treat radical prostatectomy patients if they have the OK from their urologist.

Khera: There are medicolegal considerations, and this is a new area. You have to be very careful and go through a lot of counseling with the patient. There are not enough data available yet, and more research is needed to confirm its safety.

Becker: I recommend testosterone therapy to these patients, and I take it as seriously as I do when I recommend weight loss and treatment for hypertension and dyslipidemia. Hypogonadism is a cardiovascular risk factor, and I encourage treatment.

Guay: I do not believe testosterone causes heart

disease; however, low testosterone levels may be related to heart disease. An acute vasodilatory effect of testosterone has been described in the literature, and we also know that lipid profiles improve among men with low testosterone on treatment.[15]

Mika: I have had several bodybuilders referred to me after they have given up high-dose androgens, and they do not seem to develop their own gonadal function even after 1 year.

Guay: I give these patients clomephene 50 mg three times a week, and it helps to reestablish gonadal function.

Winters: I agree that recovery from anabolic androgenic steroid use can take a very long time in some patients.

Khera: We have had the most success with human chorionic gonadotropin treatment in these patients. It takes approximately 6 months to a year to see an increase in sperm and testosterone production.

Guay: What is everyone's experience with polycythemia? It is more common in smokers, people with COPD, and occasionally, you will see a patient with primary polycythemia.

Horowitz: I virtually never see it unless we are using an injection; in noninjection therapy—the patches or gels—it is rare.

Winters: Polycythemia is related to high levels of testosterone. Although many of us would prescribe a 200-mg testosterone enanthate every 2 weeks, there are still patients who are taking 300 or 400 mg every month. Very high levels soon after the injection are problematic. PCPs need to know that 400 mg over 1 month as one injection is not the same, functionally, as 200 mg every 2 weeks.

Guay: Injections are also extremely problematic for patients with bipolar disorder.

Becker: I have had several psychiatrists ask me not to treat in that setting. A cycling bipolar patient can decompensate emotionally if subjected to widely cycling testosterone levels related to intramuscular bolusing. For this reason, I encourage these patients to accept the daily transdermal gel.

TREATMENT OPTIONS

Guay: What are the advantages of various treatment options? I think we can all agree that oral testosterone is not an option because of the methyl-testosterone debacle of the past. Oral testosterone undecanoate, however, is not associated with liver problems, but has never been approved in the United States due to erratic absorption. There are skin problems associated with transdermal testosterone. Does anyone use the Striant testosterone buccal system (Columbia Laboratories, Inc., Livingston, NJ)?

Becker: Of the 12 patients I had who tried it, only two continued, and one actually liked it—he had achieved the highest blood concentrations of testosterone.

> "I was zero for three in my trial of the buccal system; patients complained that it was uncomfortable and it would not stay in place."
>
> —Dr. Mika

Mika: I was zero for three in my trial, patients complained that it was uncomfortable and it would not stay in place.

Horowitz: We did the initial trials with it, and patient acceptance was actually quite high. I have one or two patients who have continued on it. We did not see any issues with gingivitis, which was a potential concern.

Guay: Twice-daily dosing is a problem with the buccal system—no patient wants to do anything twice a day. A new injection form of testosterone undecanoate (Nebido; Bayer/Schering AG, Berlin) that is given intramuscularly every 3 months, has completed phase 3 Food and Drug Adminitration trials; it is already available in numerous countries.

In Massachusetts, we have a lot of Medicare patients who cannot afford the gels or patches, and we give them injections. Although many patients on injections can do it themselves at home, this particular injection will probably need to be done in the office. It could be approved within 1 year.

Khera: Is it safe to say that most of you use the gels? What is your experience with AndroGel (testosterone

MONITORING MEN RECEIVING TESTOSTERONE THERAPY

1. Evaluate the patient 3 months after treatment starts and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects.

2. Monitor testosterone levels 2 or 3 months after initiation of testosterone therapy:

• Therapy should aim to raise serum testosterone levels into the mid-normal range.

• Injectable testosterone enanthate or cypionate: Measure serum testosterone levels midway between injections. If testosterone is >700 ng/dL (24.5 nmol/L) or <350 ng/dL (12.3 nmol/L), adjust dose or frequency.

• Transdermal patch: Assess testosterone levels 3 to 12 hours after application of the patch; adjust dose to achieve testosterone levels in the mid-normal range.

• Buccal testosterone bioadhesive tablet: Assess levels immediately before or after application of fresh system.

• Transdermal gel: Assess testosterone level any time after patient has been on treatment for at least 1 week; adjust dose to achieve serum testosterone levels in the mid-normal range.

• Oral testosterone undecanoate:* Monitor serum testosterone levels 3 to 5 hours after ingestion.

• Injectable testosterone undecanoate:* Measure serum testosterone level just prior to each subsequent injection and adjust the dosing interval to maintain serum testosterone in mid-normal range.

3. Check hematocrit at baseline, at 3 months, and then annually. If hematocrit is >54%, stop therapy until hematocrit decreases to a safe level; evaluate the patient for hypoxia and sleep apnea and reinitiate therapy with a reduced dose.

4. Measure bone mineral density of lumbar spine and/or femoral neck after 1 to 2 years of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture, consistent with regional standard of care.

5. Perform digital rectal examination and check PSA level before initiating treatment, at 3 months, and then in accordance with guidelines for prostate cancer screening depending on the age and race of the patient.

6. Obtain urological consultation if there is:

• Verified serum PSA concentration >4.0 ng/mL.

• An increase in serum PSA concentration >0.75 ng/mL within any 12-month period of testosterone treatment.

• A PSA velocity of >0.4 ng/mL per year using the PSA level after 6 months of testosterone administration as the reference (only applicable if PSA data are available for a period exceeding 2 years).

• Detection of a prostatic abnormality on digital rectal examination.

• An American Urilogical Association or International Prostate Symptom Score of >19.

7. Evaluate formulation-specific adverse effects at each visit:

• Buccal testosterone tablets: Inquire about alterations in taste and examine the gums and oral mucosa for irritation.

• Injectable testosterone esters (enanthate and cypionate): Ask about fluctuations in mood or libido.

• Testosterone patches: Look for skin reaction at the application site.

• Testosterone gels: Advise patients to cover the application sites with a shirt and to wash the skin with soap and water before having skin-to-skin contact, because testosterone gels leave a testosterone residue on the skin that can be transferred to a woman or child who might come in close contact. Serum testosterone levels are maintained when the application site is washed 4 to 6 hours after application of the testosterone gel.

*Not approved for clinical use in the United States.

Source: Endocrine Society Guidelines

gel 1%; Solvay, Brussels) versus Testim? Are you seeing similar efficacy results?

Mika: What is the panel's experience with regard to efficacy using AndroGel 5-gm dose? I find that about one-third of my patients need a higher dose. I have been underwhelmed with efficacy.

Horowitz: I just assume my diabetic men are going to need more. Anecdotally, I have not seen a difference between the preparations, based on total testosterone levels.

Winters: Monitoring treatment of men with type 2 diabetes again speaks to the issue of total versus free testosterone, but in this case, the issue is what value should be used to monitor therapy. There is much less information available on this issue.

Guay: We have been using calculated free testosterone for 5 or 6 years to diagnose and monitor. The total and our calculated free correlate with each other. On treatment, if I have a patient with a level of 450 or 475 ng/dL, and he says he is still not feeling well after 6 months, I readdress the symptoms and

the differential diagnosis. It is possible that it is not the low testosterone and that there is something else going on (see *Monitoring Men Receiving Testosterone Therapy*).

Horowitz: I will inch patients up into the higher range of normal. If someone has a level of 450 ng/dL and if he has symptoms, I might give him more and see he feels better. Does anyone have an issue with doing that?

Guay: My issue is that we do not have great data on thresholds. Also, we have to consider that in some cases, we may be feeding the patient's psychological neurosis about what his symptoms are.

Becker: With thyroid treatment, we know mean thyroid-stimulating hormone is 1.5 mIU/L in the middle of the bell-shaped population curve. With testosterone, we really do not understand what the mean is. As with most cases of hormone replacement therapy, I believe we do better to treat to the middle of a bell-shaped population curve than to the fringes of the normal range.

Guay: It is clearly a clinical decision made on a case-by-case basis. We each do what we do based on our clinical experience and our laboratory. As we mentioned earlier, you have to know your lab.

Khera: Our head-to-head study of Testim versus AndroGel[16] looked at 370 patients taking testosterone replacement over 3 years. We found that 20% (75 patients) had to switch preparations, the majority switched from AndroGel to Testim. The main reason was poor efficacy (94%) based on testosterone levels—patients were not getting absorption. When they switched, levels went up approximately 100 ng/dL, and that was in patients taking a 10-gm dose. The absorption of AndroGel was not as good as Testim, therefore I start everyone on Testim.

AndroGel creates a film that is absorbed over 5 to 6 hours, and Testim, because of a different transdermal enhancer, is absorbed in 1 to 2 hours.

CONTRAINDICATIONS TO THERAPY

Guay: Contraindications to testosterone therapy include breast and prostate cancer—although we have moderated with regard to prostate cancer. I know OSA is on the package insert, but I do not believe treatment aggravates it. Liver dysfunction is also a contraindication on labeling, and we have not seen anyproblems with that either.

Becker: It raises a potential medicolegal issue if it is in the labeling as a contraindication.

Winters: I think OSA is the most controversial of the warnings because so many men with OSA have low testosterone levels and are obese.

Becker: As long as OSA patients are being treated with continuous positive airway pressure, testosterone therapy is perfectly safe.

With regard to other patient populations, should patients taking atypical antipsychotics have their testosterone levels checked?

Guay: Yes. Psychiatric patients and osteoporosis patients.

Becker: In the hypogonadal osteoporotic male, if you give testosterone replacement as his antiresorptive therapy, do you have to add an alternative antiresorptive therapy?

Guay: I recommend biphosphonate if the patient has had a fracture. When their bones are back, I then withdraw it.

> "Another population that might benefit from testosterone therapy is women with Addison's disease who do not have DHEA."
> — Dr. Becker

Becker: Another population I would like to address is women with Addison's disease who do not have dehydroepiandrosterone (DHEA). When they become menopausal and lose ovarian function, they like to get their androgen-related energy back.

Guay: A German study of women with Addison's disease showed they did well with DHEA and androgen therapy.[17] Women are a different issue—the rejection of the androgen patch really affected this field.

I am concerned about media perception in the area of testosterone therapy. It appears as though the media sees our specialty as overtreating low testosterone; prescriptions are going up over the years, etc.

Plus, there is the added issue of bodybuilders and sports figures using illegal steroids. I say, look at the HIM data showing the prevalence of hypogonadism, and we are still undertreating the disease.

Mika: I think to some extent, there is the same argument in the diabetes field.

Winters: I think the risks and benefits of androgen replacement in women have not been well elucidated.

Guay: Concerning testosterone treatment of older men, the Institute of Medicine (IOM) says we should not conduct a large study to answer the risk-benefit question. The IOM wanted more baseline data before they would approve such a study. We do not even know normal testosterone ranges by age—there is so much we do not know.

Winters: If a large study were undertaken, how do you monitor for prostate cancer? Urologists have argued that PSA levels are not sufficient, and they advocate prostate biopsy. However, is it realistic to propose that healthy men who are untreated controls undergo surveillance biopsy to compare with testosterone-treated men? It would also be very costly to do so. Is it sufficient to monitor PSA and perform digital rectal exams (DREs), and how proficient are nonurologists in performing DREs?

Khera: This is a very important point. This is a new area and a new field, so we are designing this as we go along. I would argue that monitoring PSA is integral to the treatment of patients with testosterone replacement. Performing a biopsy prior to treatment is not considered the norm; most urologists would not biopsy before therapy. You have to follow the PSA. Most of the prostate cancer we detect today is not based on DREs, but rather age-sensitive PSA and velocity.

A nomogram has to be developed for patients on testosterone replacement therapy, because the change in PSA may be different. It is an evolving field, and we are still trying to get those numbers. I emphasize counseling and vigilance when you are treating these patients with testosterone replacement therapy. ■

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CME QUESTIONS

1. A Harris poll of 522 men aged ≥39 years revealed that what percentage did not know one symptom of hypogonadism?

a. 95%
b. 50%
c. 75%
d. 91%

2. According to the discussion, which of the following statements are true with regard to the MMAS?

a. It is a longitudinal study
b. The authors used cutoffs of testosterone <200 ng/dL or 200–400 ng/dL with symptoms.
c. It showed that symptom score and testosterone levels do not correlate.
d. All of the above.

3. Which of the following statements applies to the Endocrine Society's algorithm?

a. If testosterone is <200 to 300 ng/dL, a free testosterone measure should be taken.
b. A testosterone level of <230 ng/dL should be treated regardless of symptoms.

4. The HIM study found:

a. A 38% prevalence of hypogonadism
b. 30% of treated patients were undertreated
c. Both (a) and (b)
d. None of the above

5. The ADAM and IAM questionnaires have good specificity for detemining hypogonadism.

a. True
b. False

6. Which of the following are high-risk groups for low testosterone? People with:

a. Obesity
b. Diabetes
c. Chronic renal insufficiency
d. All of the above

7. Which of the following is NOT a sign associated with low testosterone?

a. Decreased energy
b. Diminished libido
c. Increased sense of well-being
d. Sleep disturbances

8. A head-to-head trial of Testim and AndroGel found:

a. Patients preferred the efficacy of AndroGel
b. Testim had better absorption
c. Most patients who switched therapies switched from Testim to AndroGel
d. Testosterone levels increased with AndroGel

9. OSA is one of the most controversial contraindications of testosterone replacement therapy.

a. True
b. False

10. Which of the following are conditions associated with increased SHBG concentrations?

a. Aging
b. Hepatic cirrhosis
c. Anticonvulsant use
d. HIV
e. All of the above

Review of ENDOCRINOLOGY
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