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How Would You Manage This Male Patient With Hypogonadism?

Grand Rounds Discussion From Beth Israel Deaconess Medical Center

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Male hypogonadism is defined as an abnormally low serum testosterone concentration or sperm count. As men age, often in the context of obesity and other comorbid conditions, serum testosterone levels may decrease. Normalizing serum testosterone levels in male adults with hypogonadism may improve symptoms related to androgen deficiency, but controversies exist regarding the long-term benefits and risks of hormone supplementation in this setting. In 2020, the American College of Physicians published a clinical guideline for the use of testosterone supplementation in adult men based on a systematic review of available evidence. Among their recommendations were that clinicians discuss whether to initiate testosterone treatment in men with age-related low testosterone with sexual dysfunction who want to improve sexual function and not initiate testosterone treatment in men with age-related low testosterone to improve energy, vitality, physical function, or cognition. Here, two clinicians with expertise in this area, one a generalist and the other an endocrinologist, debate the management of a patient with sexual symptoms and a low serum testosterone level. They discuss the diagnosis of male hypogonadism, the indications for testosterone therapy, its potential benefits and risks, how it should be monitored, and how long it should be continued.

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Mr. T is a 40-year-old man who presented with lethargy, decreased libido, and erectile dysfunction in 2016. His serum testosterone was 4.2 nmol/L (121 ng/dL) (reference range, 9.8 to 27.76 [280 to 800]). A repeat specimen obtained in the morning was also low at 4.8 nmol/L (138 ng/dL). Luteinizing hormone, follicle-stimulating hormone, and thyroid-stimulating hormone levels were normal. Sex hormone–binding globulin was 21 nmol/L (reference range, 14 to 48) and calculated free testosterone level was 135.3 pmol/L (39 pg/mL) (reference range, 208 to 642 [60 to 185]). The patient was referred to the endocrinology clinic for consultation regarding testosterone replacement therapy.

The patient's medical history includes hypertension, diabetes mellitus, atrial fibrillation, dilated cardiomyopathy, gout, obstructive sleep apnea, severe obesity, vitamin D insufficiency, and hyperlipidemia. His father had hypertension and diabetes mellitus, his mother had hypertension, and a brother has hypertension and sleep apnea. There is no family history of prostate cancer.

Medications include acetazolamide, furosemide, insulin (glargine and lispro), lisinopril, metformin, metoprolol, rivaroxaban, simvastatin, and vitamin D supplement. The patient works as a mechanical manager for a rail service. He is married and has fathered 4 children. The patient has a remote history of alcohol use. He has never smoked cigarettes, and there is no history of drug use.

Physical examination showed blood pressure of 106/64 mm Hg, pulse of 72 beats/min and regular, respirations

ABOUT BEYOND THE GUIDELINES

Beyond the Guidelines is a multimedia feature based on selected clinical conferences at Beth Israel Deaconess Medical Center (BIDMC). Each educational feature focuses on the care of a patient who "falls between the cracks" in available evidence and for whom the optimal clinical management is unclear. Such situations include those in which a guideline finds evidence insufficient to make a recommendation, a patient does not fit criteria mapped out in recommendations, or different organizations provide conflicting recommendations. Clinical experts provide opinions and comment on how they would approach the patient's care. Videos of the patient and conference, the slide presentation, and a CME/MOC activity accompany each article. For more information, visit www.annals.org/GrandRounds.

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that were unlabored, and weight of 127.5 kg (281 lb) with a body mass index of 42.6 kg/m^2. He had no gallops or murmurs; lungs were clear to percussion and auscultation; abdomen was soft, nontender, and without organomegaly; and extremities were without edema. His hematocrit was 31.3, leukocyte count was 7.2×10^9 cell/L, platelet count was 347×10^9 cells/L; glucose was 5.8 mmol/L (104 mg/dL), blood urea nitrogen/creatinine were 1945/115 μmol/L (22/1.3 mg/dL), alanine aminotransferase/aspartate aminotransferase were 21/22 IU/L, total cholesterol level was 51 mmol/L (198 mg/dL) with a low-density lipoprotein component of 25 mmol/L (95 mg/dL), hemoglobin A_{1c} was 5.8%, and vitamin D level was 57 nmol/L (23 ng/mL).

Intramuscular testosterone cypionate, once a week, was started, and the patient initially noticed modest improvement in libido and erectile dysfunction. His treatment course was complicated by mild erythrocytosis. There was no effect on his sleep apnea or other chronic medical conditions. Testosterone treatment was discontinued in 2019 because of the patient's "fear of needles." More recently, the patient and his wife have noticed recurrence of diminished libido, and he has expressed an interest in restarting treatment.

MR. T'S STORY (VIDEO AT ANNALS.ORG)

See the Patient Video (**Video 1**, available at Annals.org) to view the patient telling his story.

I was primarily started on testosterone therapy because I was experiencing low libido. I was experiencing lethargy and was just not as active as I used to be. My doctor told me that, in a man of my age, sometimes the testosterone level dips. He explained my options, but my main concern was exposure to my wife or my daughter from the gel, and so I decided to use injections. The injections were self-administered, but I had some training in the doctor's office as to how to give them.

My doctor told me that testosterone would boost my energy level and libido, and that I would start feeling more myself than I was at the time. We discussed the initial risks, but to be honest with you, I don't recall many of them. My primary care physician did explain that I would need occasional blood tests just to monitor the levels of the testosterone and make sure that it wasn't having any negative effects. The benefits of the testosterone therapy were an increased libido and increased energy level. From my experience thus far, there have been no side effects from taking testosterone therapy.

I stopped taking the testosterone more so because I have a great fear of needles, and I did not like injecting myself every week. Afterwards, my wife noticed a lessening of my libido. My wife had a conversation with me about the reduced attraction to her, and so I asked my doctor about other forms of treatment that I could pursue rather than the needles.

CONTEXT, EVIDENCE, AND GUIDELINES

Male hypogonadism is defined as an abnormally low serum testosterone level or sperm count. These findings can result from disease of the testes (primary hypogonadism) or disease of the pituitary gland or hypothalamus (secondary hypogonadism). As men age, often in the context of obesity and other comorbid conditions, serum testosterone levels may decrease. In the United States, the incidence of low testosterone is estimated to be 20% in men older than 60 years, 30% in those older than 70 years, and 50% in those older than 80 years (1). Men with low serum testosterone levels may be asymptomatic or have sexual (for example, decreased libido, erectile dysfunction) or nonspecific (for example, fatigue, decreased energy level, depression) symptoms, or a mix of sexual and nonspecific symptoms. Normalizing serum testosterone levels in male adults with hypogonadism may improve some of these symptoms, but controversies exist about the long-term benefits and risks of using exogenous testosterone in these patients.

In 2020, the American College of Physicians (ACP) published a clinical guideline for the use of testosterone supplementation in adult men based on a systematic review of available evidence (2). The review identified 38 randomized, controlled trials that met inclusion criteria to evaluate the benefits and risk of testosterone treatment. The mean age of participants was 66 years, and follow-up ranged from 6 to 36 months. Participants in most studies had a mean baseline total testosterone level of 10.41 nmol/L (300 ng/dL) or lower. Clinical outcomes were evaluated by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system and included sexual function, physical function, quality of life, energy and vitality, depression, cognition, serious adverse events, major adverse cardiovascular events, and other adverse events.

The ACP guideline recommendations are summarized in **Table 1** (2). Low-certainty evidence from 7 trials showed a small improvement in quality of life (standardized mean difference [SMD], 0.33 lower [95% CI, 0.50 to 0.16 lower]). Moderate-certainty evidence from 7 trials showed a small improvement in global sexual function (SMD, 0.35 higher [CI, 0.23 to 0.46 higher]), and low-certainty evidence from 7 trials showed a small improvement in erectile function (SMD, 0.27 higher [CI, 0.09 to 0.44 higher]). Low-certainty evidence from 7 trials showed little to no difference in physical function as assessed by objective measures (SMD, 0.14 higher [CI, 0.02 to 0.27 higher]).

Low-certainty evidence from 14 trials showed a small increase to no difference in cardiovascular events (Peto odds ratio, 1.22 [CI, 0.66 to 2.23]). Moderate-certainty evidence from 8 trials found no evidence of increased risk for other serious adverse events (Peto odds ratio, 0.92 [CI, 0.73 to 1.21]). Individual trials were not powered to detect mortality differences, whereas pooled analysis of 12 studies showed fewer deaths among patients who received testosterone compared with placebo (Peto odds radio, 0.47 [CI, 0.25 to 0.89]). However, the clinical guidelines committee determined there was insufficient evidence to make conclusions about mortality. Evidence from 20 observational studies with a mean follow-up of 0.73 to 10.3 years showed no increased risk in mortality, cardiovascular events, prostate cancer, or thromboembolic disease.

CLINICAL QUESTIONS

To structure a debate between our 2 discussants, we mutually agreed on the following key questions to consider when applying this guideline to clinical practice and to Mr. T in particular:

Question 1: How is male hypogonadism diagnosed, and what are the indications for testosterone?

Question 2: What are the potential benefits and risks of testosterone therapy?

Question 3: How should testosterone therapy be monitored, and how long should it be continued?

Our discussants' general approach to men with sexual symptoms and possible hypogonadism is provided in the Figure.

DISCUSSION

Viewpoint: Marc L. Cohen, MD

Question 1: How is male hypogonadism diagnosed, and what are the indications for testosterone?

Male hypogonadism, as defined by the Endocrine Society, is symptoms and signs of testosterone deficiency in combination with "unequivocally and consistently low" serum testosterone levels (3). A decreased frequency of morning erections, decreased frequency of sexual thoughts, and erectile dysfunction are the symptoms most suggestive of hypogonadism in middle-aged and older men (4). Infertility, gynecomastia, low bone mineral density, and sweats/hot flushes are also suggestive of the diagnosis, whereas changes in mood, energy, concentration, sleep, and body composition are nonspecific. While secondary sex characteristics may be affected in younger men, physical findings are often not present in older individuals (3).

Definitions of "normal" testosterone levels have varied through the years and between organizations (5). Both the American Urologic Association and the Endocrine Society currently advocate a cutoff of 10.41 nmol/L (300 ng/dL) for an abnormally low total testosterone level (3, 5, 6). As testosterone levels have a diurnal rhythm with peak values in the morning (7) and can be lowered by food intake, blood should be drawn in the morning after an overnight fast. Values should be obtained on at least 2 separate mornings, as there can be significant day-to-day variability. Up to 30% of men with an initial abnormal testosterone level have a normal value on repeat testing (3). Total testosterone is a sufficient test to identify hypogonadism in young, healthy men, but it is less accurate in older men or those with comorbid conditions that affect sex hormone–binding globulin (SHBG) (7), in whom clinicians should also order free testosterone (8). Glucocorticoids (daily doses equal to 15 mg of prednisone or higher) can suppress testosterone levels within 3 days, and levels can also be decreased by systemic illness, eating disorders, drug misuse, excessive exercise, opioid analgesics, and ketoconazole (9). Testosterone supplementation is indicated in patients with symptoms of hypogonadism and abnormally low total or free testosterone levels on at least 2 morning samples in whom the benefits are likely to outweigh potential risks.

Table 1. ACP's Testosterone Treatment Guideline Recommendations*

Recommendation 1a: ACP suggests that clinicians discuss whether to initiate testosterone treatment in men with age-related low testosterone with sexual dysfunction who want to improve sexual function (conditional recommendation; low-certainty evidence). The discussion should include the potential benefits, harms, costs, and patient's preferences.
Recommendation 1b: ACP suggests that clinicians should reevaluate symptoms within 12 months and periodically thereafter. Clinicians should discontinue testosterone treatment in men with age-related low testosterone with sexual dysfunction in whom there is no improvement in sexual function (conditional recommendation; low-certainty evidence).
Recommendation 1c: ACP suggests that clinicians consider intramuscular rather than transdermal formulations when initiating testosterone treatment to improve sexual function in men with age-related low testosterone, as costs are considerably lower for the intramuscular formulation and clinical effectiveness and harms are similar.
Recommendation 2: ACP suggests that clinicians not initiate testosterone treatment in men with age-related low testosterone to improve energy, vitality, physical function, or cognition (conditional recommendation; low-certainty evidence).

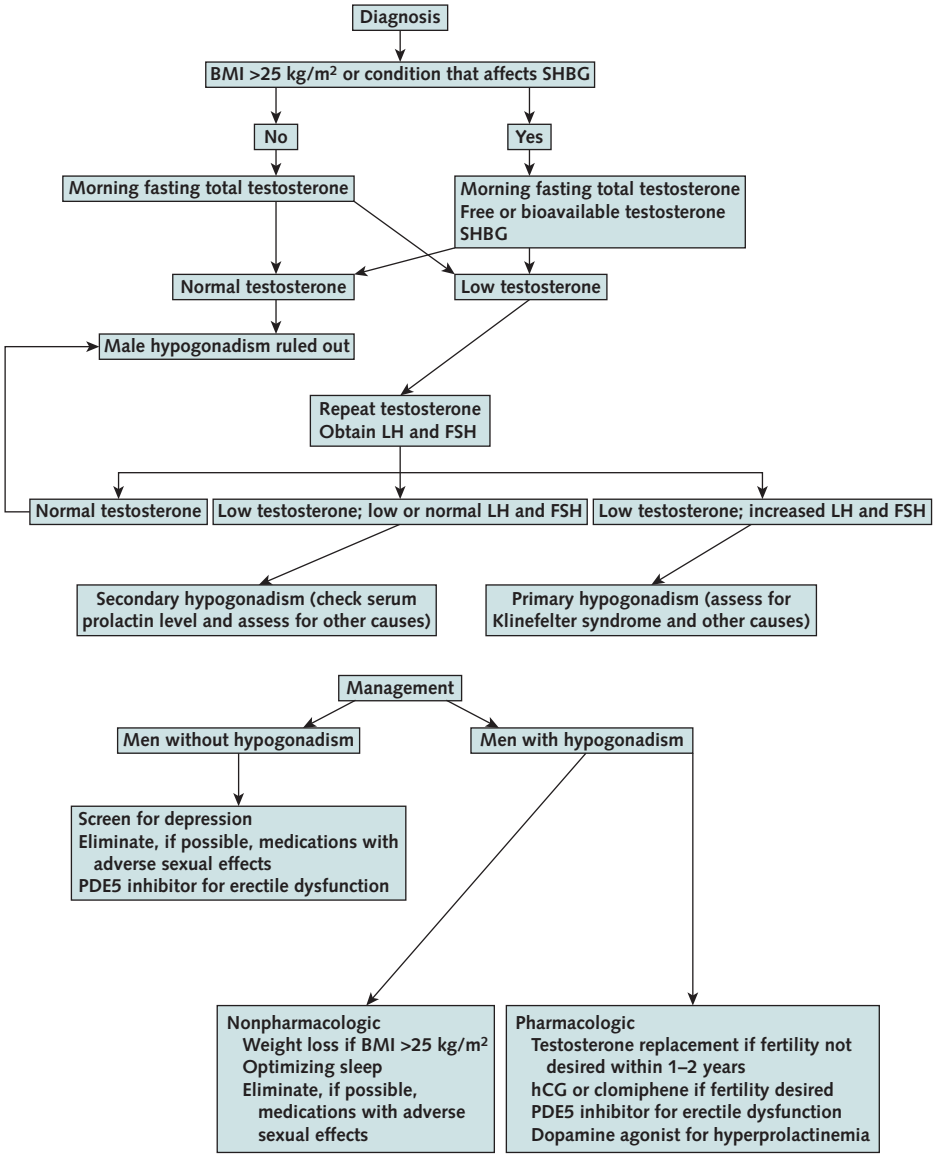
ACP = American College of Physicians.
* Data from reference 2.

Question 2: What are the potential benefits and risks of testosterone therapy?

Testosterone replacement therapy (TRT) results in small but significant improvements in erectile function, libido, and sexual satisfaction (10), as well as in anemia, bone mineral density, and lean body mass. Evidence has been inconclusive regarding its impact on cognitive function, mood, energy, and quality of life (3, 6, 11). Exogenous testosterone can suppress spermatogenesis, and thus for men for whom fertility remains important, alternate approaches to symptom management are preferred. Testosterone replacement therapy is also contraindicated in patients with active prostate or breast cancer; its impact on the development of prostate cancer has been less clear (3). Testosterone can cause an increased hematocrit level from stimulation of erythropoiesis (10) and is contraindicated in patients with baseline erythrocytosis. Caution is also advised in patients with congestive heart failure, given TRT's potential to cause salt and water retention (3, 12), as well as in patients with obstructive sleep apnea.

The potential cardiovascular benefits and risks of TRT remain unclear: Individual studies and meta-analyses have yielded conflicting results. Some epidemiologic studies have demonstrated an inverse relationship between testosterone levels and cardiovascular morbidity and mortality (12), although this finding may simply reflect the association between cardiovascular risk factors (for example, obesity, metabolic syndrome) and their negative effects on SHBG. One cohort study showed a relative risk for myocardial infarction (MI) of 1.36 after TRT (13), while another (14) associated TRT with a reduction in all-cause mortality, MI, and stroke. The Testosterone in Older Men Trial, a randomized, placebo-controlled, double-blind trial that was stopped early by its safety monitoring board because of concerns about cardiovascular effects found 22% of participants in the intervention group had

Figure. General approach to men with sexual symptoms and possible hypogonadism.



BMI = body mass index; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; LH = luteinizing hormone; PDE5 = phosphodiesterase type 5; SHBG = sex hormone–binding globulin

cardiovascular-related events, compared with 5% in the placebo group (15). A 2017 randomized controlled trial found TRT increased coronary artery plaques (16). A 2013 article found cardiovascular-related events were more likely to be associated with testosterone replacement in trials not funded by the pharmaceutical industry (17). Nonrandomized studies are limited by confounding factors, and randomized trials have been underpowered or have used proxy markers of cardiovascular disease rather than clinical outcomes, or both. A joint report from the American Association of Clinical Endocrinology and the American College of Endocrinology concluded there is "no compelling evidence that TRT either increases or decreases cardiovascular risk" (18). It recommended individual review of risk versus benefit and called for large-scale, prospective, randomized controlled trials focusing on cardiovascular risk (18). The large placebo-controlled TRAVERSE trial with such a focus is currently underway (19).

Question 3: How should testosterone therapy be monitored, and how long should it be continued?

Both total testosterone level and hematocrit should be checked within 3 to 6 months of beginning therapy and at least annually while the patient is receiving treatment. Timing of phlebotomy depends on the method of administration (Table 2) (20). Short-acting injectable testosterone can often cause supraphysiologic levels within

24 to 48 hours after injection, with levels gradually declining to low-normal range over 2 weeks (9, 21). A mid-cycle level is generally used for monitoring, although obtaining peak (18 to 36 hours after injection) and trough (just before next injection) levels provide additional information. In patients receiving daily topicals (gels and patches), levels can be checked 3 to 8 hours after the last application following 1 week of use (6). While there may be day-to-day variability, 1 or 2 measurements generally allow maintenance of dosing within a safe range (22). Levels (postdose for topicals and midcycle for injectables) should be targeted to the middle of the laboratory reference range. Improvement in sexual symptoms with TRT is generally seen within 3 months once a physiologic level is achieved (11); if not, discontinuing the treatment should be considered.

The effect of erythrocytosis on blood viscosity and platelet aggregation means erythrocytosis increases the risk for thrombosis and cardiovascular disease (12, 23). Erythrocytosis occurs more commonly in men who receive testosterone through injection than through other routes (44% vs. 15% in one study [24]) and in men older than 60 years (9). For patients with a hematocrit of 54% or higher, treatment should be paused until levels return to normal and then restarted at a lower dose (3, 9).

Regarding Mr. T, although his symptoms and laboratory results are suggestive of true hypogonadism, only one of the samples was obtained in the morning, and ideally a second fasting morning testosterone sample would confirm hypogonadism. His follicle-stimulating hormone level is inappropriately normal given his level of testosterone, which suggests secondary hypogonadism. Although his presentation is most likely the result of the combined effects of obesity and age, I would check a prolactin level and ask about symptoms and signs of a sellar lesion. If there were any findings of concern, pituitary imaging would be advisable.

Before restarting TRT for Mr. T, I would strongly encourage an attempt at weight loss through lifestyle changes, potentially supported by pharmacotherapy or surgical intervention. Obesity has a clear association with hypogonadism, and weight loss can lead to significant increases in testosterone levels (25, 26). In addition to this potentially reversible secondary cause of hypogonadism, the patient has comorbid conditions, including congestive heart failure and obstructive sleep apnea, which may increase the risks of testosterone replacement.

While recognizing the significant cost implications and respecting the rationale behind the ACP's recommendation to consider injection therapy before other methods, I would prescribe transdermal gel to Mr. T, partially in deference to his stated wishes. To minimize cost impact, I would choose a generic formulation. Gels are generally better tolerated than patches, given the high rates of skin irritation with patches (up to 60% of patients, with 5% to 10% discontinuing use) (9). Counseling the patient regarding its safe use and avoidance of skin contact with others for several hours after application is important. The potential time burden for clinicians, particularly those without a nurse or pharmacist on site, to provide teaching about needle and syringe assembly, injection technique, and appropriate needle disposal may be considerable. In addition, given Mr. T's multiple cardiovascular risks and the greater likelihood of erythrocytosis on injection therapy, transdermal testosterone may provide a better benefit–risk ratio.

Viewpoint: Michael S. Irwig, MD

Question 1: How is male hypogonadism diagnosed, and what are the indications for testosterone?

Male hypogonadism refers to the inability of the testes to produce adequate androgens, sperm, or both. Although this definition appears straightforward, no consensus exists regarding what constitutes adequate or normal testosterone production. Clinicians generally rely on the lower limit of the reference range for serum testosterone, which is defined as the 2.5th percentile for lean healthy adult men younger than 40 years. Depending on the assay, this number historically has ranged between 250 and 350 ng/dL [8.7 to 12.1 nmol/L]. This approach has several problems and limitations. First, the 2.5th percentile is an arbitrary statistical cut point that is not based on symptoms. Second, the one-size-fits-all reference range does not take into account lower serum testosterone concentrations in older men and in men who are overweight or obese (27). In the Massachusetts Male Aging Study, the 2.5th percentile for total testosterone was 8.7 nmol/L (251 ng/dL) for men in their 40s and 5.4 nmol/L (156 ng/dL) for men in their 70s (28). In the European Male Aging Study, mean concentrations of total testosterone and free testosterone were 5.1 nmol/L (147 ng/dL) and 53.785 pmol/L (15.5 pg/mL) lower, respectively, in men with obesity compared with men of normal weight (29).

An overreliance on the "normal" reference range has led to an epidemic of male hypogonadism diagnoses, which can be attributed to increased rates of obesity and testing. In a sample of men with obesity and diabetes mellitus with a mean age of 60 years, the prevalence of a subnormal free testosterone was 50% (30). This increased testing has been fueled, in large part, by a pharmaceutical marketing campaign that promotes the widely held belief that common nonspecific symptoms in men, such as fatigue, low libido, and erectile dysfunction, are caused by age-related androgen deficiency (31).

The relevant question for diagnosis is, "Below what level of testosterone do symptoms and signs of androgen deficiency occur?" Several researchers have attempted to answer this question. One elegant study assessed symptoms in older men rendered hypogonadal with the use of a gonadotropin-releasing hormone agonist in which the men were treated with different doses of testosterone (32). Significant declines in sexual desire and erectile function were only noted when serum total testosterone concentrations were less than 3.5 nmol/L (100 ng/dL). The European Male Aging Study of 2966 community-dwelling men aged 40 to 79 years found that testosterone concentrations between 8 to 11 nmol/L (230 and 317 ng/dL) or less than 8 nmol/L (<230 ng/dL) were both associated with lower estimated heel bone mineral density after adjusting for age, body mass index, smoking status, and medical comorbid conditions (33).

Excess weight is associated with lower concentrations of total testosterone due to lower concentrations of SHBG, which is the major protein carrier of testosterone. A low

Table 2. Characteristics of Testosterone Formulations*

Formulation	Available as Generic	Initial Dosage	Usual Adult Dosing	When to Monitor	Advantages	Disadvantages	Monthly Cost†
Short-acting injectable							
Testosterone cypionate (IM)	Yes	75–100 mg once weekly OR 150–200 mg every 2 wk	50–100 mg once weekly OR 100–200 mg every 2 wk	Midway, peak or trough	Inexpensive; can achieve target levels easily	Increased incidence of erythrocytosis as compared with other formulations; pain at injection site	$30
Testosterone enanthate (IM)	Yes						$56
Long-acting injectable							
Testosterone undecanoate	No	750 mg	Repeat 750 mg after 4 wk, then every 10 wk thereafter	Trough before next dose, 3–6 mo after starting therapy	Less frequent injections; dose titration not necessary; may have less testosterone level fluctuations	Large-volume IM injection (3.5 mL); small risk for pulmonary oil microembolism and anaphylaxis; patients must be observed for 30 min after injection	$1229 per 750-mg dose
Transdermal							
Gel available as 1%, 1.62%, 2%	Yes	40–50 mg once daily	10–100 mg/d	3–8 h after last dose applied; consider second time-point given day-to-day variability	Less skin irritation than patches; less erythrocytosis than injectable formulations	Risk for skin-to-skin transfer to another person if hands are not washed or if not allowed to dry; some formulations have an odor	$145–$564; most $300–$350
Patch	No	One 4-mg patch/d	2–6 mg/d	Morning level checked after evening application, about 14 d after start of therapy or dose adjustments	Convenient to use	Up to one third of patients have skin reactions	$308–$616
Solution (30 mg/actuation)	Yes	60 mg (2 pumps) once daily in the morning to axillae	30–120 mg/d (1–4 pumps)	2–8 h after applying solution, at least 14 d after starting therapy	Self-administration; administration site may be preferable to some	Risk for skin-to-skin transfer to others	$405
Other							
Buccal	No	30 mg applied every 12 h to gum above incisor	Same	Before morning dose, 4–12 wk after initiating therapy	Avoids large fluctuations in levels	16% of men have mouth and gum irritation	$815
Nasal	No	11 mg (2 pump actuations; 1 actuation per nostril) three times daily, 6–8 h apart	Same	Periodic measurement beginning 1 mo after initiating therapy		Frequent dosing; may cause nasopharyngitis; nasal/sinus inflammation and epistaxis	$825
Oral undecanoate	No in United States	237 mg twice a day	316–396 mg twice daily	4–6 h after morning dose	Oral	Twice-daily dosing before meals; increase in systolic BP	$835–$4026
Pellet	Yes	150–450 mg every 3–6 mo implanted in subcutaneous tissue	Same	Measure at end of dosing interval	Long-acting	Inability to titrate dose after pellets are implanted; inflammation and pain at pellet site; expulsion, extrusion, infection, or fibrosis of pellet	$105 per 75-mg pellet

BP = blood pressure; IM = intramuscular.
* Data from reference 20; based on U.S. medication pricing by Elsevier, accessed February 2020.
† Pricing is based on the average wholesale acquisition cost for a 30-d supply, unless otherwise indicated, for generic if available.

SHBG can often explain the discrepancy in the common scenario of a low total but normal free (or bioavailable) testosterone level. In addition, certain types of testosterone assays are more reliable than others. Liquid chromatography/mass spectrometry is considered the most accurate assay for total testosterone, with radioimmunoassays for free testosterone considered less reliable (34).

The indications for TRT can be divided into 2 broad categories: organic and functional (35). Organic hypogonadism refers to conditions with a structural or pathologic abnormality, such as Klinefelter syndrome, Kallmann syndrome, hypopituitarism, and postsurgical hypogonadism. Functional hypogonadism refers to conditions without a structural or pathologic abnormality and include obesity, opiate use, and depression. In a study of 200 adult men referred for borderline total testosterone levels between 6.9 to 12 nmol/L (200 and 350 ng/dL), 39% had overweight, 43% had obesity, and 56% had depression (36). In general, testosterone supplementation is considered standard therapy for consistently and unequivocally low testosterone levels (that is, <6.9 nmol/L [<200 ng/dL]) associated with organic causes. On the other hand, the benefit–risk ratio of TRT for men with functional hypogonadism and borderline low testosterone levels is unknown. The best management of men with functional hypogonadism may be by addressing the underlying cause. For example, weight loss for obese men may increase or normalize endogenous testosterone levels, while improving cardiovascular health and other associated comorbid conditions, such as hypertension, hyperlipidemia, and obstructive sleep apnea (35). Other nonpharmacologic approaches include a trial of withdrawing medications that have adverse sexual effects, the use of phosphodiesterase type 5 inhibitors for erectile dysfunction, and optimizing sleep (37).

Question 2: What are the potential benefits and risks of testosterone therapy?

In men with consistently and unequivocally low testosterone levels, TRT can have clear benefits with improved sexual function, body composition, and bone health. Low bone density in hypogonadal men is often related to estrogen deficiency, because less testosterone is available for conversion to estradiol by aromatase. The benefits of TRT for men with borderline low levels are uncertain, because many of the common nonspecific symptoms are usually unrelated to androgen concentrations. A systematic review of testosterone treatment in men found moderate-certainty evidence for a small improvement in global sexual function and low-certainty evidence for little to no difference in physical function (38). It is important to counsel potential users of TRT to have realistic expectations of its potential benefits.

Short-term risks of TRT are well-known and include infertility, hypertension, acne vulgaris, edema, erythrocytosis, and a lower high-density lipoprotein cholesterol level (3). Less is known about the long-term risks of TRT because large, randomized controlled trials have not been conducted. Clinicians are often concerned about the potential adverse effects of testosterone on the prostate. Although testosterone can fuel metastatic prostatic cancer, there is no evidence that TRT increases the risk for new or low-grade prostate cancer (39). Testosterone therapy often increases the prostate-specific antigen (PSA) and the detection of subclinical prostate cancer related to increased surveillance. In a study of older men treated for 12 months, the mean PSA increased by 0.47 μg/L (SD, 1.1) (0.47 ng/mL [SD, 1.1]) (40). A meta-analysis found that TRT does not worsen lower urinary tract symptoms in hypogonadal men compared with placebo (41).

Regarding risks associated with TRT, there is a growing problem of off-label misuse of testosterone by eugonadal men to improve muscle mass and sexual health (42). This problem is, in large part, driven by private for-profit clinics that promote testosterone for antiaging purposes. When men receiving testosterone therapy transfer care, it is important for the new practitioner to assess the circumstances that led to testosterone initially being prescribed and to determine whether adequate baseline testing was performed to establish the diagnosis of hypogonadism.

Question 3: How should testosterone therapy be monitored, and how long should it be continued?

Monitoring TRT can be challenging. One strategy to guide dosing of the short-acting intramuscular testosterone esters is to obtain a trough testosterone level 0 to 2 days before an injection (Table 2). Another strategy is to obtain a midcycle testosterone level, which could be at 6 to 8 days after an injection if the medication is administered every 2 weeks. I would aim for a trough testosterone level around 8.7 to 12.1 nmol/L (250 to 350 ng/dL) and a midcycle level around 15.6 to 22 nmol/L (450 to 650 ng/dL). Titrating the dose in men receiving topical gels can also be a challenge because of large variations in serum testosterone levels after application. One study found that a 2-hour postapplication testosterone level one day was a poor indicator of average serum testosterone level on another day (22).

For men with borderline low serum testosterone levels or functional hypogonadism, reassessment of symptoms is prudent 3 to 6 months after the start of treatment. If there is no significant improvement, the treatment should be discontinued, because the symptoms are likely unrelated to low serum androgen concentrations.

For Mr. T, I would recommend restarting TRT given his several unequivocally low testosterone levels less than 5.2 nmol/L (150 ng/dL) and his recurrent sexual symptoms. Short-acting testosterone esters, which are administered intramuscularly or subcutaneously, are the most cost-effective option. For example, the retail cost of a 12-month supply of testosterone cypionate is approximately $200 versus $900 for a generic gel and $5000 for a branded gel.

Nonetheless, it is uncertain whether TRT will improve Mr. T's sexual symptoms, which was his primary motivation to resume therapy. It is likely that his erectile dysfunction is multifactorial and related to aging, vascular disease from hypertension and hyperlipidemia, adverse effects from his antihypertensive medications, or a combination of these factors. However, even if TRT does not improve his symptoms, one could argue that it should be restarted to improve his anemia and to maintain bone health.

SUMMARY

In 2020, the ACP published a clinical guideline for the use of testosterone supplementation in adult men based on a systematic review of available evidence (2). Among the recommendations were that clinicians discuss whether to initiate testosterone treatment in men with age-related low testosterone with sexual dysfunction who want to improve sexual function and not initiate testosterone treatment in men with age-related low testosterone to improve energy, vitality, physical function, or cognition.

Mr. T presented in 2016 with lethargy, decreased libido, and erectile dysfunction in the setting of hypertension, diabetes mellitus, atrial fibrillation, congestive heart failure, gout, obstructive sleep apnea, severe obesity, vitamin D insufficiency, and hyperlipidemia. As part of his evaluation, a serum testosterone test was performed and the level was found to be low. The patient began testosterone cypionate intramuscularly once a week and initially noticed modest improvement in libido and erectile function. His treatment course was complicated by mild erythrocytosis. He stopped using testosterone in 2019 because of a stated "fear of needles." More recently, he and his wife have noticed recurrence of diminished libido, and he has expressed an interest in restarting treatment.

Dr. Cohen states that he would obtain a second fasting morning testosterone level to confirm the diagnosis of hypogonadism. He would strongly encourage an attempt at weight loss with lifestyle changes, potentially supported by pharmacotherapy or surgical intervention, before restarting TRT. In addition to this potentially reversible secondary cause of hypogonadism, the patient has comorbid conditions, such as congestive heart failure and obstructive sleep apnea, which may increase the risks associated with testosterone replacement. If TRT were reinitiated, Dr. Cohen would be more likely to prescribe transdermal gel to this particular patient, partially in deference to his stated wishes, and, to minimize cost impact, he would choose a generic formulation.

Dr. Irwig recommends restarting TRT in Mr. T given several unequivocally low testosterone levels and his multiple comorbid conditions. He would recommend short-acting testosterone esters, which are administered intramuscularly or subcutaneously, as the most cost-effective option. However, Dr. Irwig is uncertain whether TRT will improve Mr. T's sexual symptoms. It is likely that his erectile dysfunction is multifactorial and related to aging, vascular disease, and adverse effects from antihypertensive medications. Even if TRT does not improve his symptoms, one could argue that it should be restarted to improve his anemia and for maintenance of bone health.

GRAND ROUNDS CONFERENCE (VIDEO AT ANNALS.ORG)

A transcript of the audience question-and-answer period is available in the **Appendix** (available at Annals.org). To view the conference video (**Video 2**), including the question-and-answer session, go to Annals.org.

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Appendix: Comments and Questions

Dr. Gerald Smetana: I know one of the issues that came up this morning was about prostate cancer risk, and I am curious about your take on that. I find when I discuss this issue with my own patients, frequently this is the game-changer that leads people to choose not to take testosterone, because they are worried about the prostate cancer risk. How confident can we be about the data that there is no risk unless prostate cancer is already known to be present?

Dr. Marc Cohen: Yes, I would agree with you that in my conversations with patients this is often something that we discuss a lot. I think there are two components to this. First is the risk and whether to consider testosterone, and the second is whether to then monitor, which is an even more controversial and complicated issue. For the first, I think there really are not conclusive data one way or another. As Michael said, there haven't been great large trials looking at that particular outcome over a period of time, and as to prostate cancer risk, as we know, we're looking at decades of potential risk. So, that can be really challenging. I would say I often have conversations with my patients about their personal risk for prostate cancer. I wouldn't say that we know that there is a risk, but I think we don't know that there is not a risk. So, if somebody came to me with 2 first-degree relatives with prostate cancer and this was a concern of theirs, I would certainly have a much more extended conversation about the lack of clear data, and the fact that prostate cancer can be a hormone-responsive cancer. That being said, in considering both the goals of testosterone therapy and the rationale for not believing that there is an increased risk, we are really trying to return men to physiologic testosterone levels; we're not trying to get to supraphysiologic levels. So, you could argue, "Are we really increasing risk if we're just bringing patients to be at what we would consider to be a normal testosterone level?" So, that's the argument on the other side. I think we just don't know. I don't think we can tell patients that we have a lot of certainty either way.

Dr. Smetana: Dr. Irwig, do you share that view? Or would you differ in any way in the way that you counsel your own patients?

Dr. Michael Irwig: So, there's basically so much that we don't know about this because we don't have the large, long-term, randomized controlled trials. However, we do have many decades of prescribing testosterone to millions of men, so we do have a lot of good data, and there does not seem to be an increased signal in either prostate cancer or in cardiovascular events. So we definitely do want to bring it up, and it is a balancing game of how symptomatic somebody is. If somebody is not that symptomatic, then they may not want to go on this therapy; whereas some patients may say, "Listen, I feel so symptomatic, I am willing to accept a potential small increased risk if my quality of life increases." So, it really needs to be individualized.

Dr. Smetana: Thank you both. Next we're going to move onto our question-and-answer session. I am going to be reading the questions and will give both of our discussants an opportunity to answer. I am going to start with a question from Dr. Mark Zeidel, our Department Chair at the Department of Medicine at Beth Israel Deaconess Medical Center. Dr. Zeidel asked, "Were the clinical trials of testosterone placebo-controlled? You can imagine that the injections themselves could have a significant placebo effect."

Dr. Irwig: Yes, I am happy to take that one on. There have been randomized controlled trials, and most of them have been performed on older men, and this is really the only way to tease out some of these symptoms, but I can tell you from a clinical standpoint that I think there is a big placebo effect. It is not uncommon for men who I have prescribed testosterone to, or who have been on testosterone, to tell me, "Listen, for the first month or two things were great, and I noticed an improvement in my energy and libido, but then after a few months it just stopped working." So, that leads me to believe that there may be some placebo effect for a lot of men who do get on the testosterone.

Dr. Smetana: Okay. The next question is from Dr. Russ Phillips, Dr. Phillips is a colleague in our Division of General Medicine at Beth Israel Deaconess Medical Center. Dr. Phillips asks, "Should we be checking bone density in patients who have hypogonadism, who do not opt for testosterone therapy?"

Dr. Cohen: I can share what I generally do in practice, and I would be very interested to hear Michael's take on this as well. I often do—if I have found that someone has biochemical evidence of persistently low testosterone or hypogonadism, screen them with a bone density. I don't necessarily follow that and repeat it over time if normal, but I do at one point try to assess it. I am more likely to do that, though, in my frail older men. If I have a younger man that I do not believe is a high fall risk who is getting lots of weight-based exercise, I don't universally screen those men; but certainly in older men that have evidence, and particularly if I am worried about frailty, I will.

Dr. Irwig: It's an excellent question, and some of the data shows that low bone density is associated with a total testosterone only when it gets less than 200 ng/dL [6.94 nmol/L], and the stronger correlate to bone density is actually estradiol rather than testosterone. Estrogen is very protective for bone in men, as well. So, I would consider measuring an estradiol level in men, and the most accurate way to measure estradiol is by liquid chromatography mass spectrometry. It's also the most accurate way to measure total testosterone levels as well. So, in men who have a low estradiol level or a low total testosterone of less than 200 [ng/dL; 6.94 nmol/L], that would certainly be an indication to screen with a bone density test.

Dr. Smetana: The next question is from Dr. Douglas Kiel who is a gerontologist at BIDMC. Dr. Kiel asks, "Is there any significance to the observation of normal pituitary LH [luteinizing hormone] and FSH [follicle-stimulating hormone] in the setting of low testosterone?" And we had another related question, which is, "When should you think about central hypogonadism?"

Dr. Irwig: You definitely want to check the gonadotropins in the diagnosis. So just to recap the diagnosis, one of the things that we encounter all the time is that you always have to wonder whether the diagnosis was made correctly, and particularly if the patient comes to you as a new patient and they have been on testosterone, you should delve into how was the diagnosis made? Did they have multiple testosterone levels that were both low? Were the LH and the FSH checked? Normally, most men who do have low testosterone levels do have LH and FSH levels that are either normal or low, and this is considered secondary hypogonadism. It is quite uncommon to see the primary causes. I don't happen to follow LH and FSH in men on testosterone therapy.

Dr. Cohen: Just to reinforce, I think it is important—we didn't talk a lot about this—but when you're initially making the diagnosis to check an FSH and LH to rule out any other causes, and if there are any abnormalities, considering a prolactin or doing a screening by history for symptoms that would suggest a prolactinoma or concern in the pituitary, you don't want to miss those diagnoses. So I think that it is an important teaching point that the FSH and LH should be checked when you're initially making the diagnosis.

Dr. Smetana: Our next question is from another colleague of ours in General Medicine, Dr. Gila Kriegel. Dr. Kriegel asks—and I think this is a matter of opinion, but I would be curious to see what you both think, "Which patients with hypogonadism should be referred to an endocrine consultant?" Because I think a lot of this can be done safely in the primary care setting.

Dr. Cohen: So, I can answer that. I agree that many men can be managed in the primary care setting. I will say that for age-related hypogonadism, or what we're describing as functional hypogonadism, I am more likely to manage those myself, whereas if there is a secondary cause or other abnormalities of an endocrinologic axis, I generally involve an endocrinologist. I also would say, I mentioned earlier the issue about fertility; there are other ways to manage testosterone levels that don't require testosterone replacement, and if fertility is an issue, you're going to use other agents that may stimulate spermatogenesis. And so for that, which I do believe is a bit more complicated and not something we do commonly in primary care, I refer all of those patients to endocrine.

Dr. Smetana: All right, our next question, and either of you can address this, is "Can you discuss some of the newer testosterone formulations? Such as, for example, the subcutaneous pellets or the nasal spray?" Again, this would bring up the issue of what's appropriate in primary care or not. What is your take on those?

Dr. Irwig: So, there are a lot of new formulations that are out there. We have a long-acting testosterone undecanoate; we have a nasal spray that needs to be administered 2 to 3 times a day; we have testosterone pellets the size of a grain of rice that are subcutaneously implanted into the fat, typically into the buttock, and those can last for several months; we have a buccal testosterone, which is a tablet that you place above the incisor tooth and it gets absorbed through the gums twice a day. Having said that, very few patients are actually on some of these formulations because this is driven by the insurance companies, the copays, and the tiers. So, a lot of these testosterone formulations are not covered, and the costs would be prohibitively expensive. So rather than paying a copay of, say $30 or $40 a month for a gel, somebody would have to pay hundreds of dollars if they wanted to get on the one of the newer formulations. All of these have their pros and cons. I am not a particular fan of the nasal spray because it has to be dosed 2 to 3 times a day and there are a lot of adherence issues with a medication that needs to be taken that frequently. I am not a fan of the pellets because it involves an invasive procedure where you need to inject local anesthesia—tunnel a trocar under the skin; there can be infections and extrusion. The other major problem with the pellets is that once you put them in, you can't take them out. It's like mini golf, you can overshoot or you can undershoot. I have been called by a doctor who said, "Listen, I have a guy who had testosterone pellets, and his serum testosterone level is 3000, what do I do?" Well, you can't go in and just take them out, so you don't have that same flexibility. Most of the men in our practices are on the injectable testosterones, or on the topical gels for the most part.

Dr. Smetana: The next question relates to erythrocytosis. So, you both mentioned monitoring for that, what do you do if that actually occurs? If the hematocrit does become too high, is that a contraindication to continuing this? Or is there any nuanced way of adjusting the dosing where you can come up with a compromise?

Dr. Cohen: First of all, if you go above a hematocrit of 54, you would hold therapy. Often you would pause therapy, and then redose at a lower dose. Your goal is to try to achieve therapeutic testosterone levels while having hematocrit remain normal. There are somewhat rare situations when patients, for whatever reason, may require a certain dose of testosterone to get to a therapeutic level, but have erythrocytosis at that level, and some practitioners will have patients donate blood or do an intermittent phlebotomy to tolerate a higher dose. I don't generally do that very often in practice, but I know that some specialists would do that. Generally, you would adjust the dose to try to balance getting a therapeutic response while avoiding the side effect.

Dr. Smetana: And we have one last question for you. You both talked about the variability of testosterone levels with age, that is, the age-adjusted norms. Why do clinical labs not adjust for age? And should we be considering that when we decide whether a level is truly low or not?

Dr. Irwig: I certainly think so. I don't think it's appropriate to take a 70-year-old overweight man and say, "Your testosterone is lower than that of a 30-year-old," the same way we wouldn't take a postmenopausal woman and say, "Well, your estrogen level isn't like that of a 30-year-old woman", or your growth hormone level. So, I think we should be age-adjusting, and one of the other things about testosterone variability that is a good teaching point is that testosterone levels are not always higher in the morning every day. This is only if you look at multiple days over multiple patients. An analogy is temperature. The average temperature on March 11 is higher than the average temperature on February 11 if you look at all of the years, but in any particular year, that may not be the case.

Dr. Smetana: I want to thank you both for a lively discussion in our Q&A. I am going to go back now to Dr. Libman, who will conclude our presentation this morning.