SUPPLEMENT TO
THE JOURNAL OF
FAMILY PRACTICE

FREE 1.0 CME CREDIT

Available at jfponline.com

VOL 59, NO 7 / JULY 2010

Late-onset male hypogonadism and testosterone replacement therapy in primary care

CASE STUDY. Mr Williams, a 61-year-old overweight male with type 2 diabetes mellitus (T2DM), is being seen by his primary care physician to follow up for his diabetes management. Over the past 8 to 10 months, Mr Williams has felt tired and occasionally experienced difficulty focusing at work. Titration of his glucose-lowering medications has not improved his symptoms. He has noted a weight gain of 4 pounds over the past 5 months.

Definition and classification

Mr Williams' tiredness and difficulty concentrating could be a result of his T2DM and its management or numerous other causes, including late-onset male hypogonadism (LOMH). LOMH is a subset of male hypogonadism, which is a disorder caused by the inability of the testes to produce physiologic levels of testosterone and the normal number of spermatozoa as a result of a disruption of the hypothalamic-pituitary-gonadal axis.[1] There are 2 types of male hypogonadism, regardless of age of onset. *Primary* involves testicular failure that results in low testosterone levels, impairment of spermatogenesis, and elevated gonadotropin levels. *Secondary* results from central defects of the hypothalamus or pituitary and is associated with low-to-normal

Stephen A. Brunton, MD, FAAFP
Adjunct Clinical Professor
Department of Family Medicine
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

Richard Sadovsky, MD
Associate Professor
Family Medicine
State University of New York
Downstate Medical Center
Brooklyn, New York

This supplement to *The Journal of Family Practice* was supported by an educational grant from Endo Pharmaceuticals, Inc., and was submitted by the Primary Care Education Consortium. It has been edited and peer reviewed by *The Journal of Family Practice*.

LEARNING OBJECTIVES

After completing this activity, the primary care clinician will be better able to:

1. Define and broadly classify late-onset male hypogonadism
2. Describe the epidemiology of late-onset male hypogonadism
3. Describe the key signs and symptoms suggesting late-onset male hypogonadism
4. Identify the role of lab measurements, including total testosterone (T), free T, and bioavailable T, in the clinical diagnosis
5. List the goals of testosterone replacement therapy for late-onset male hypogonadism
6. List the factors to consider in selecting patients for testosterone replacement therapy
7. Describe the similarities and differences of the testosterone replacement therapy delivery systems
8. Identify a strategy to monitor safety and efficacy of, as well as patient adherence with, testosterone replacement therapy

TARGET AUDIENCE

Family physicians and clinicians who have an interest in treating patients with late-onset male hypogonadism.

SPONSOR DISCLOSURE STATEMENT

As a continuing medical education provider accredited by the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of the Primary Care Education Consortium (PCEC) to require any individual in a position to influence educational content to disclose the existence of any financial interest or other personal relationship with manufacturer(s) of any commercial product(s).

The content collaborators at the PCEC report that there are no existing financial relationships to disclose.

Dr Brunton disclosed that he is on the speakers bureaus of Boehringer-Ingelheim and Novo Nordisk, Inc. He is on the advisory boards for Amylin Pharmaceuticals, Inc., Kowa Pharmaceuticals America, Inc., and Novo Nordisk, Inc.

Dr Sadovsky disclosed that he is on the advisory board for Endo Pharmaceuticals, Inc.

The medical accuracy reviewer for this activity, Martin M. Miner, MD, disclosed that he is on the speakers bureaus of Auxilium Pharmaceuticals, Inc. and Boehringer-Ingelheim. He receives contracted research support from GlaxoSmithKline.

The CME reviewer for this activity, Allan J. Wilke, MD, has no real or apparent conflicts of interest to report.

CONFLICT OF INTEREST STATEMENT

When individuals in a position to control content have reported financial relationships with one or more commercial interests, PCEC works with them to resolve such conflicts to ensure that the content presented is free of commercial bias. The content of the publication was vetted by the following mechanisms and modified as required to meet this standard:

- Content peer review by an external topic expert
- Content peer review by an external CME reviewer
- Content validity by internal PCEC clinical editorial staff

OFF-LABEL DISCLOSURE STATEMENT
In accordance with ACCME guidelines, the faculty authors have been asked to disclose discussion on unlabeled or unapproved uses of drugs during the course of the activity.

ACCREDITATION STATEMENT
The Primary Care Education Consortium is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education through the Primary Care Education Consortium.

The Primary Care Education Consortium designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Release date: July 1, 2010
Expiration date: July 1, 2011

MEDIUM
CME text publication in the form of a journal article.

SPONSORSHIP STATEMENT
This program is sponsored by the Primary Care Education Consortium.

SUPPORTER STATEMENT
This activity is supported by an educational grant from Endo Pharmaceuticals, Inc.

METHOD OF PHYSICIAN PARTICIPATION
To receive CME credit, please read the journal article and, upon completion, go to: **www.pceconsortium.org/JFPJuly2010TRT** and complete the online evaluation to receive your certificate of completion.

PRIMARY CARE EDUCATION CONSORTIUM

gonadotropin levels (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) and low testosterone levels. Appropriate hormonal stimulation restores fertility in secondary but not primary hypogonadism.[1] Testosterone replacement in hypogonadal men can actually decrease fertility by decreasing gonadotropin production and lowering sertoli cell production of sperm.

As defined by an international consensus panel representing several endocrine organizations, LOMH is ". . . a clinical and biological syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels."[2] While there is no age cut-off for LOMH, and adult men younger than age 60 years can develop LOMH, the majority of those who meet the diagnostic criteria for low testosterone are older than 60 years. Although testosterone declines with age, it declines at different rates among different men and among those with different chronic conditions. These variations can lead to distressing and disabling conditions.

The symptomatic overlap of LOMH with other disorders makes the diagnosis of LOMH difficult, which can lead to underdiagnosis and lack of treatment. The Boston Area Community Health Survey found that 5.5% of a random sample of men age 30 to 79 years (N=1486) had a testosterone level <300 ng/dL and at least 1 symptom of hypogonadism, but were not being treated. Conversely, 0.8% of men who had a testosterone level <300 ng/dL and at least 1 symptom of hypogonadism were being treated for hypogonadism.[3]

The prevalence of LOMH has been estimated to range from 9% to 39%, depending on the laboratory and clinical criteria used.[4,5] The Baltimore Longitudinal Study on Aging found that the prevalence increased with age, rising from <10% in men under age 49 years to 12% of men in their 50s, 19% of men in their 60s, 28% of men in their 70s, and 49% of men in their 80s.[5] While a declining testosterone level is a normal part of aging, only a portion of men develop the symptoms of LOMH and meet the diagnostic criteria. This is analogous to osteoporosis and lumbar spinal stenosis. Thus, while not a disorder found exclusively in men older than age 60, LOMH is far more prevalent in older than in younger men.

Conditions in which there is a high prevalence of a low testosterone level include radiation therapy; a mass or other disease of the sellar region; use of medications with antiandrogen properties, such as glucocorticoids, ketoconazole, and opioids; end stage renal disease and maintenance dialysis; moderate-to-severe chronic obstructive lung disease; human immunodeficiency virus (HIV)-related weight loss; infertility; osteoporosis or low-trauma fracture, especially in young men; dyslipidemia; hereditary hemochromatosis; T2DM or metabolic syndrome; tobacco use; malnutrition; or obesity.[1,6-9] A strong inverse relationship has been observed between the incidence of metabolic syndrome and testosterone levels (total and unbound, or "free"), as well as the sex hormone binding globulin (SHBG) level. The association is strongest for the dyslipidemia and waist circumference components of metabolic syndrome when compared with elevated triglycerides, hypertension, or glucose intolerance.[9]

CASE STUDY. The history reveals that Mr Williams began to notice a loss in his libido about 2 years ago, although he has not experienced any erectile dysfunction. He thought that this symptom was related to his T2DM, so he had not thought much of it until his wife voiced her concern a few weeks ago. Mr Williams reports that he has been walking and using the stairs more at work because he has "put on a few pounds" over the past year. He indicates that he has been sleeping well and has not been depressed. He admits to feeling frustrated at times while working around the house, as he has found he does not have the strength to do some of the things he used to do. For example,

he had some difficulty moving an extension ladder while painting the second story of his house a few weeks ago.

On physical examination, there was no evidence of gynecomastia or galactorrhea. Mr William's testes measured approximately 3.5 cm x 2.5 cm and he has diminished facial hair. The remainder of the physical exam was relatively unremarkable, with no retinopathy. His vital signs and reflexes were normal.

Diagnosis

As noted earlier, the nonspecific nature of the symptoms of LOMH present a challenge in the diagnosis. Consequently, the diagnosis of LOMH is based on both signs and symptoms and laboratory tests.

History and physical examination

Some signs and symptoms are suggestive of male hypogonadism, while others are less clearly associated. (**TABLE 1**)[1] While no clear relationship between decreasing testosterone level and symptoms has been determined, Zitzmann et al did observe a general trend between decreasing testosterone level and increasing prevalence of groups of symptoms. (**FIGURE**)[10] As experienced by Mr Williams, loss of libido and loss of vigor are the two symptoms often experienced first as testosterone levels decline with advancing age.

To facilitate taking the history, several questionnaires that focus on signs and symptoms of hypogonadism in postpubertal men were developed.[11-13] Two examples are the Androgen Deficiency in Aging Males (ADAM) by Morley et al,[11] which has been used for a decade, and a more recent questionnaire developed by Rosen et al.[13] The ADAM questionnaire consists of 10 questions that assess several domains of importance in diagnosing hypogonadism in men aged 40 years or older. The Rosen questionnaire assesses 7 domains: (1) physical function; (2) bodily signs and symptoms; (3) sexual function and libido; (4) sleep function; (5) mood and affective function; (6) memory and cognitive function; and (7) distress or bother associated with hypogonadism symptoms. Although helpful, the use of questionnaires is limited by the variability in symptoms among men with LOMH.

A directed physical examination complements the history. The amount and distribution of body hair, including the beard, should be assessed and losses such as male pattern baldness should be noted. The presence and extent of gynecomastia, as well as galactorrhea, which suggests hyperprolactinemia, should be evaluated. The size, firmness, and consistency of the testes should be noted, with shrinkage or softness suggesting hypogonadism. Although the prostate should be examined, it may be enlarged in older men, despite a low testosterone level.[14]

TABLE 1 Symptoms and signs of androgen deficiency in men[1]

Suggestive
• Incomplete sexual development, eunuchoidism, aspermia
• Reduced sexual desire (libido) and activity
• Decreased spontaneous erections
• Breast discomfort, gynecomastia
• Loss of body (axillary and pubic) hair, reduced shaving
• Very small, soft or shrinking testes (especially <5 mL) (normal adult volume is 20 to 30 mL)
• Inability to father children, low or zero sperm counts
• Height loss, low trauma fracture, low bone mineral density
• Reduced muscle bulk and strength
• Hot flushes, sweats
Association less clear
• Decreased energy, motivation, initiative, aggressiveness, self-confidence
• Feeling sad or blue, depressed mood, dysthymia
• Poor concentration and memory
• Sleep disturbance, increased sleepiness
• Mild anemia (normochromic, normocytic, in the female range)
• Increased body fat, body mass index
• Diminished physical or work performance

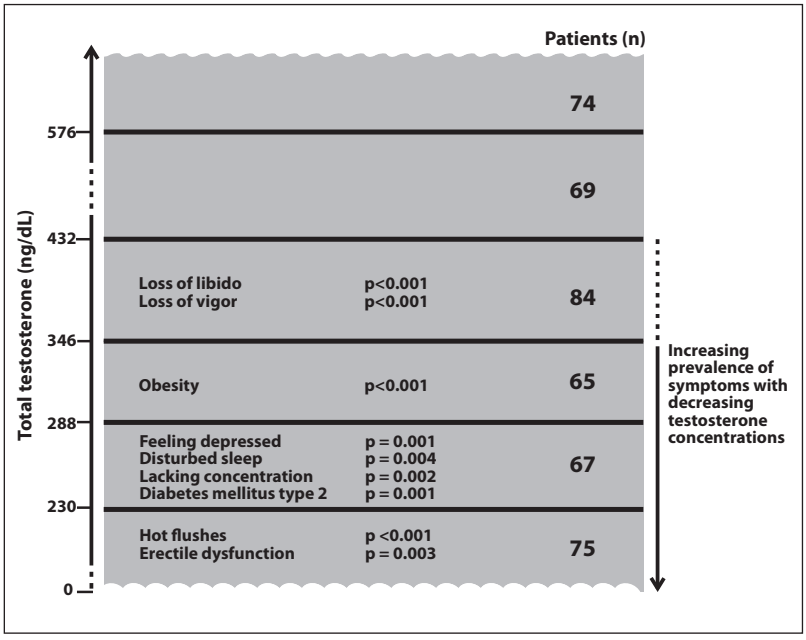
Adapted with permission. Copyright 2006, the Endocrine Society.

Laboratory testing

Laboratory testing is essential to confirm a clinical diagnosis of LOMH, as well as to differentiate primary from secondary hypogonadism. Measurement of the serum total testosterone level is the easiest means of screening for LOMH. The total testosterone level includes 3 fractions: free, weakly bound to albumin, and tightly bound to SHBG. In young adult men, the average percentages are 2%, 68%, and 30%, respectively. Testosterone that is free or weakly bound to albumin constitutes biologically available testosterone.[14]

The total testosterone level should be drawn between 7:00 AM and 11:00 AM, as it is highest at this time of day.[2] The American Association of Clinical Endocrinologists identifies a total testosterone level below 200 ng/dL as low,[14] while The Endocrine Society identifies 300 ng/dL as the threshold.[1] An abnormal result necessitates a repeat test. If the testosterone level is confirmed as being low, LH and FSH levels should be obtained to differentiate

FIGURE General correlation between increasing symptom prevalence and decreasing testosterone level[10]



Adapted with permission. Copyright 2006, The Endocrine Society.

CASE STUDY. Mr Williams' blood test revealed the following:

- Total testosterone level: 285 ng/dL; repeat: 276 ng/dL. (normal: ≥300 ng/dL)
- FSH level: 19 IU/L (normal: 1.0-12.0 IU/L)
- LH level: 13 IU/L (normal: 2.0-14.0 IU/L)

Based on these laboratory results and Mr Williams' signs and symptoms, he is given a diagnosis of male hypogonadism, probably LOMH type.

primary from secondary hypogonadism.[1,14] Since the amount of testosterone that is biologically available is affected by the level of SHBG, measuring the free testosterone level is more useful than the total testosterone level when the SHBG level is outside of the normal range (which increases by about 1% per year beyond the age of 30 years or so).[14] Measurement of SHBG may be useful in men with conditions that might alter SHBG levels and, therefore, impact the actual bioavailable testosterone level. Older age, hepatic cirrhosis, hyperthyroidism, anticonvulsants, estrogens, and HIV infection are associated with an elevated SHBG level, while obesity, hypothyroidism, nephrotic syndrome, and some medications (glucocorticoids, progestins, and androgens) lower the SHBG level.[1] Some experts advocate confirmation of hypogonadism with a free testosterone analysis, but complex standardization and interpretation issues make this of limited practical use.

In men with a total testosterone level below 200 ng/dL and either a low LH or elevated prolactin level, which suggests secondary hypogonadism, magnetic resonance imaging (MRI) of the pituitary may be useful to exclude pituitary or hypothalamic tumors. MRI may also be considered in older men with secondary hypogonadism if (a) the total testosterone level is <150 ng/dL and the LH level is low-to-normal or the prolactin level is increased; or (b) panhypopituitarism, persistent hyperprolactinemia, or symptoms such as visual changes or headache are present.[1]

Treatment

The combination of signs and symptoms of LOMH and a low testosterone level confirms the diagnosis of LOMH and is an indication to consider testosterone replacement therapy (TRT). Other factors must be considered to determine if TRT is appropriate for a specific individual. First, contraindications to TRT must be carefully investigated. TRT is not recommended for men with a history of breast cancer, untreated prolactinoma, a palpable prostate nodule or induration, or prostate-specific antigen (PSA) level >3 ng/mL.[1,2,14] While a history of prostate cancer has been considered an absolute contraindication to TRT[2], 3 retrospective studies have demonstrated TRT to not result in PSA recurrence in up to 12 years following radical retropubic prostatectomy.[15-17] In these patients, it is recommended that TRT be provided by a urologist or oncologist. Other conditions in which TRT is not recommended include erythrocytosis (hematocrit >50%), severe benign prostatic hyperplasia (BPH) (American Urological Association [AUA] score >19), uncontrolled severe heart failure (New York Heart Association III/IV), or untreated obstructive sleep apnea.[1,2,14] Caution is advised for those with risk factors for obstructive sleep apnea, such as obesity or chronic lung disease, and those who have a history of myocardial infarction or coronary artery disease.[18,19] Finally, along with a discussion of the anticipated benefits and risks of treatment, discussion of the need for chronic treatment and regular monitoring should be undertaken with the patient prior to initiating TRT.

The second factor to discuss with the patient is that the goals of TRT are to restore physiologic concentrations of testosterone to the normal range, as well as to induce and maintain secondary sex characteristics and to improve sexual function, sense of well-being, behavior, and bone mineral density.[1,14]

The third factor is to confirm the type(s) and impact

TABLE 2 Clinical pharmacology of some testosterone formulations[1]

Formulation	Regimen	Pharmacokinetic profile	Advantages	Disadvantages
T enanthate or cypionate	100 mg/wk IM or 200 mg every 2 wk IM	After a single IM injection, serum T levels rise into the supraphysiologic range, then decline gradually into the hypogonadal range by the end of the dosing interval	Corrects symptoms of androgen deficiency. Relatively inexpensive, if self-administered. Flexibility of dosing	Requires IM injection. Peaks and valleys in serum T levels
Nongenital transdermal system	1 or 2 patches, designed to nominally deliver 5-10 mg T over 24 h applied daily on nonpressure areas	Restores serum T, DHT, and E2 levels into the physiological male range	Ease of application, corrects symptoms of androgen deficiency and mimics the normal diurnal rhythm of T secretion. Lesser increase in hemoglobin than injectable esters	Serum T levels in some androgen-deficient men may be in the low-normal range; these men may need application of 2 patches daily. Skin irritation at the application site may be a problem for some patients
T gel	5-10 g T gel containing 50-100 mg T should be applied daily	Restores serum T and E2 levels into the physiological male range	Corrects symptoms of androgen deficiency, provides flexibility of dosing, ease of application, good skin tolerability	Potential of transfer to a female partner or child by direct skin-to-skin contact; moderately high DHT levels
Buccal, bioadhesive, T tablets	30 mg controlled release, bioadhesive tablets used twice daily	Absorbed from the buccal mucosa	Corrects symptoms of androgen deficiency in healthy, hypogonadal men	Gum-related adverse events in 16% of treated men
T pellets	Four to six 200-mg pellets implanted SC	Serum T peaks at 1 mo and then sustained in normal range for 4 to 6 mo	Corrects symptoms of androgen deficiency	Requires surgical incision for insertions; pellets may extrude spontaneously

E2, estradiol; DHT, dihydrotestosterone; T, testosterone.

Adapted with permission. Copyright 2006, The Endocrine Society.

of current symptoms, since not all signs and symptoms respond to TRT. Sexual symptoms and loss of libido generally require higher levels of testosterone repletion, while fatigue requires lower levels. In addition, the impact of symptoms must be weighed against the risks and costs of treatment.

Efficacy of TRT

More than 5 decades of data and clinical experience has demonstrated TRT's ability to restore the blood testosterone level to the normal range and to improve a variety of other physiologic signs and symptoms. While TRT is effective in restoring the testosterone level, it should not be assumed that the initial dosage level will be successful in doing so. Grober et al observed that more than half of men treated had a total testosterone level <300 ng/dL with initial TRT.[20] Consequently, increasing the dose is generally required to achieve the target testosterone level and improve symptoms. This can often be accomplished within several months, after which time the level usually remains stable over several years.[21]

Numerous other benefits of TRT have been demonstrated, including improvements in libido, sexual function, bone mineral density, lean and fat body mass, and mood.[21-27]

Other benefits are possible, but conflicting study results or limited evidence make them less certain. These include possible improvements in cognition, quality of life, muscle strength, glycosolated hemoglobin level, insulin resistance, and the lipid profile.[22-24,28-36]

Adverse events and risks

Evidence supporting the long-term safety of TRT has come primarily from clinical experience, as long-term studies have generally been limited to a few years of follow up. Hepatotoxicity is no longer a concern because the oral formulations that caused it are not available in the US. More common adverse events associated with TRT include acne and oily skin, as well as reduced spermatogenesis and fertility.[1] A 10% to 15% increase in the hemoglobin and/or hematocrit level is also commonly observed; the latter may increase the risk for a thromboembolic event.[1,21,29,37,38]

Uncommon adverse events associated with TRT are gynecomastia, male pattern baldness, hypertension, and worsening symptoms of BPH. For example, gynecomastia was observed in 2.5% and urinary symptoms (eg, nocturia, hesitancy, and urgency) in 3.7% of men treated with AndroGel over 3 years.[38] Obstructive sleep apnea or severe congestive heart failure also can be worsened with TRT.[1] Edema may occur in patients with preexisting cardiac, renal, or hepatic disease.

Concern regarding TRT has primarily focused on the prostate and the fear of causing prostate cancer. While small increases in the PSA level have occasionally been observed in hypogonadal men taking TRT,[22,35] an international multidisciplinary panel concluded that in men without prostate cancer, "there is no conclusive evidence that testosterone therapy increases the risk of prostate cancer or benign prostatic hypertrophy . . . or will convert subclinical prostate cancer to clinically detectable prostate cancer."[2] In fact, analysis by a different panel of 18 prospective studies involving 3886 men with incident prostate cancer and 6438 control subjects found no association between the risk of prostate cancer and serum concentrations of testosterone, free testosterone, and several other related hormones, with the exception of an inverse relationship with SHBG.[39] Similarly, a study involving 44 hypogonadal men (aged 44 to 78 years) found no treatment-related change in prostate histology, median prostate levels of testosterone and dihydrotestosterone, gene expression, or cancer incidence or severity following 6 months of treatment with testosterone.[40]

In men with locally advanced and/or metastatic prostate cancer, the international multidisciplinary panel concluded that "there is unequivocal evidence that testosterone can stimulate growth and aggravate symptoms."[2] However, as noted earlier, TRT has been successfully utilized in men following radical retropubic prostatectomy.[15-17] Nonetheless, these recommendations point to the importance of laboratory testing prior to and during TRT. In addition, urological consultation should be considered if prostate abnormalities are detected,[1] such as an AUA BPH symptom index score greater than 19, as this is suggestive of severe prostate symptoms.[41]

When the clinician and patient have thoroughly discussed the risk-benefit ratio of TRT and appropriate expectations and requirements for replacement, a decision can be made about the type of TRT formulation to be used.

Testosterone formulations

The injectable, implantable, dermal, transdermal, and buccal testosterone formulations currently available in the US are safe and effective.[2] The availability of several formulations for TRT enables individualization based on patient preference, dosing and monitoring requirements, adverse events, and cost. (**TABLE 2**)[1]

Three testosterone formulations that permit dosing less frequently than every day are available, which may be advantageous where daily administration is problematic. Two of these, the cypionate (Depo-Testosterone, generics) and enanthate (Delatestryl, generics) formulations, are administered via intramuscular injection and the third is available as implantable pellets (Testopel) placed every 4 to 6 months. While the intramuscular formulations are usually given every 1 to 2 weeks, wide fluctuations in the blood testosterone level occur between doses. Consequently, unwanted physiologic and emotional effects (eg, breast tenderness, hyperactivity, fatigue, depression, or anger) may be observed.[42] Initiating therapy with a low dose and titrating slowly may lessen such unwanted effects.

Testosterone can be applied to the skin either as a gel or as a patch. The gel formulations (Androgel or Testim) are used more widely than other formulations of testosterone in the US. However, the 2 gel formulations are not interchangeable, principally because they are not bioequivalent[43] and can produce different clinical and biochemical responses.[20] Androgel is available in 2 forms (pump or packet) and can be applied to the shoulder, upper arm, or abdomen. Testim is available in 1 form and can be applied to the shoulder or upper arm. The prescribing information for the gel formulations includes a black box warning concerning secondary exposure, as there is a risk of contact transmission with the gel.[19,38] The transdermal patch (AndroDerm) provides close approximation to the normal circadian plasma concentration of testosterone when applied in the evening.[44] Should minor skin irritation occur, the use of a 0.1% triamcinolone cream (not ointment) applied prior to patch replacement can be helpful without affecting testosterone absorption.[44]

A buccal formulation (Striant) applied twice daily causes testosterone to be absorbed through the buccal mucosa, thereby avoiding the hepatotoxicity associated with first-pass metabolism of oral formulations.[45] Gum

TABLE 3 Monitoring testosterone replacement therapy[1,2,14,18,19,38,45,46]

What to monitor	When to monitor
Adherence	Baseline to identify potential issues, then at each visit
Adverse events—general	3 months after initiation, then annually
Adverse events—formulation-specific	Buccal: if there are taste alterations, examine gums and oral mucosa for irritation Injectable: inquire about fluctuations in mood or libido and evaluate hematocrit to detect excessive erythrocytosis, especially in older patients Patch: look for signs of skin reaction at the application site Gels: advise patients to cover the application site with clothing and wash the skin before having skin-to-skin contact because gels leave a residue of testosterone on the skin that can be transferred to a woman or child who comes in close contact
Bone mineral density (lumbar spine, femoral neck, or hip)	1 to 2 y after initiation in hypogonadal men with osteoporosis or low-trauma fracture
Hematocrit, hemoglobin	Baseline, 3 to 4 months, 12 months, then annually. If Hct >50%, stop treatment until Hct falls to safe level, evaluate for hypoxia and sleep apnea, reinitiate at reduced dose
Lipid profile	Baseline, 6 to 12 months after initiation, then annually
Liver function	Baseline, periodically
Prostate	Digital rectal examination and prostate specific antigen measurement before initiating treatment, at 3 months, then according to guidelines
Symptom response	Every 3 to 4 months after initiation, then annually
Testosterone level	Baseline Transdermal gel: after 2 weeks of treatment 3 months after initiation for: • Cypionate/enanthate: midway between injections • Transdermal patch: 4 to 8 h after patch application • Buccal tablet: immediately before application

Hct, hemocrit.

and mouth irritation, taste alteration, bitter taste, and headache are among the most common adverse events.[45]

Monitoring

The use of TRT requires baseline assessment and ongoing monitoring to prevent and reduce the adverse events and risks that may occur. Several sources provide guidance for baseline assessment and periodic monitoring for patients receiving TRT. (**TABLE 3**)[1,14,18,19,38,45,46] Recommended assessments at baseline include total testosterone, PSA, hematocrit, hemoglobin, liver enzymes, and lipid profile. These same assessments, as well as for adherence, adverse events, and symptom response, must be performed periodically following initiation of TRT. While the target total testosterone level is generally in the middle of the physiologic range of 350 to 1050 ng/dL, some men respond well to a level in the low-to-normal range. Attention should be paid to monitoring for acne, gynecomastia, and breast tenderness[1] because they can be disconcerting to the patient. Close monitoring of the prothrombin time/international normalized ratio is necessary when adding or modifying TRT in a patient being treated with an oral anticoagulant, as bleeding may occur. Similarly, blood glucose levels may be decreased in a patient with diabetes, thereby requiring closer monitoring of blood glucose.[38]

Summary

LOMH is frequently observed in primary care, with an increasing prevalence in older men. The diagnosis is based on a combination of mostly nonspecific signs and symp-

toms and measurement of testosterone and other hormones. Various testosterone formulations are available to individualize therapy to restore the physiologic testosterone level and improve symptoms. Careful assessment must be undertaken prior to and during TRT to prevent harm, reduce adverse events, and foster adherence. n

TAKE THE CME EVALUATION ONLINE:
www.pceconsortium.org/JFPJuly2010TRT

REFERENCES

1. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: An Endocrine Society Clinical Practice Guideline. http://www.endo-society.org/guidelines/final/upload/FINAL-Androgens-in-Men-Standalone.pdf. Accessed June 14, 2010.
2. Wang C, Nieschlag E, Swerdloff R, et al. Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. J Androl. 2009;30:1-9.
3. Hall SA, Araujo AB, Esche GR, et al. Treatment of symptomatic androgen deficiency: results from the Boston Area Community Health Survey. Arch Intern Med. 2008;168:1070-1076.
4. Mulligan T, Frick MF, Zuraw QC, et al. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. Int J Clin Pract. 2006;60:762-769.
5. Harman SM, Metter EJ, Tobin JD, et al; for the Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab. 2001;86:724-731.
6. Ding EL, Song Y, Malik VS, et al. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2006;295:1288-1299.
7. Mäkinen JI, Perheentupa A, Irjala K, et al. Endogenous testosterone and serum lipids in middle-aged men. Atherosclerosis. 2008;197:688-693.
8. Zmuda JM, Cauley JA, Kriska A, et al. Longitudinal relation between endogenous testosterone and cardiovascular disease risk factors in middle-aged men. A 13-year follow-up of former Multiple Risk Factor Intervention Trial participants. Am J Epidemiol. 1997;146:609-617.
9. Kupelian V, Hayes FJ, Link CL, et al. Inverse association of testosterone and the metabolic syndrome in men is consistent across race and ethnic groups. J Clin Endocrinol Metab. 2008;93:3403-3410.
10. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab. 2006;91:4335-4343.
11. Morley JE, Charlton E, Patrick P, et al. Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism. 2000;49:1239-1242.
12. Liu PY, Swerdloff RS, Wang C. Relative testosterone deficiency in older men: clinical definition and presentation. Endocrinol Metab Clin North Am. 2005;34:957-972, x.
13. Rosen RC, Araujo AB, Connor MK, et al. Assessing symptoms of hypogonadism by self-administered questionnaire: qualitative findings in patients and controls. Aging Male. 2009;12:77-85.
14. Petak SM, Nankin HR, Spark RF, et al; for the American Association of Clinical Endocrinologists. 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;8:440-456.
15. Kaufman JM, Graydon RJ. Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. J Urol. 2004;172:920-922.
16. Agarwal PK, Oefelein MG. Testosterone replacement therapy after primary treatment for prostate cancer. J Urol. 2005;173:533-536.
17. Khera M, Grober ED, Najari B, et al. Testosterone replacement therapy following radical prostatectomy. J Sex Med. 2009;6:1165-1170.
18. Delatestryl [prescribing information]. Lexington, MA: Indevus Pharmaceuticals, Inc.; 2007.
19. Testim [prescribing information]. Malvern, PA: Auxilium Pharmaceuticals, Inc.; 2009.
20. Grober ED, Khera M, Soni SD, et al. Efficacy of changing testosterone gel preparations (Androgel or Testim) among suboptimally responsive hypogonadal men. Int J Impot Res. 2008;20:213-217.
21. Wang C, Cunningham G, Dobs A, et al. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. J Clin Endocrinol Metab. 2004;89:2085-2098.
22. Wang C, Swerdloff RS, Iranmanesh A, et al; for the Testosterone Gel Study Group. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. J Clin Endocrinol Metab. 2000;85:2839-2853.
23. Kapoor D, Goodwin E, Channer KS, et al. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol. 2006;154:899-906.
24. Isidori AM, Giannetta E, Greco EA, et al. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. Clin Endocrinol (Oxf). 2005;63:280-293.
25. Bhasin S, Woodhouse L, Casaburi R, et al. Older men are as responsive as young men to the anabolic effects of graded doses of testosterone on the skeletal muscle. J Clin Endocrinol Metab. 2005;90:678-688.
26. Isidori AM, Giannetta E, Gianfrilli D, et al. Effects of testosterone on sexual function in men: results of a meta-analysis. Clin Endocrinol (Oxf). 2005;63:381-394.
27. Tracz MJ, Sideras K, Boloña ER, et al. Testosterone use in men and its effects on bone health. A systematic review and meta-analysis of randomized placebo-controlled trials. J Clin Endocrinol Metab. 2006;91:2011-2016.
28. Cherrier MM, Craft S, Matsumoto AH. Cognitive changes associated with supplementation of testosterone or dihydrotestosterone in mildly hypogonadal men: a preliminary report. J Androl. 2003;24:568-576.
29. Cherrier MM, Matsumoto AM, Amory JK, et al. Characterization of verbal and spatial memory changes from moderate to supraphysiological increases in serum testosterone in healthy older men. Psychoneuroendocrinology. 2007;32:72-79.
30. Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, et al. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. JAMA. 2008;299:39-52.
31. Simon D, Charles MA, Lahlou N, et al. Androgen therapy improves insulin sensitivity and decreases leptin level in healthy adult men with low plasma total testosterone: a 3-month randomized placebo-controlled trial. Diabetes Care. 2001;24:2149-2151.
32. Kenny AM, Prestwood KM, Gruman CA, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci. 2001;56:M266-M272.
33. Lu PH, Masterman DA, Mulnard R, et al. Effects of testosterone on cognition and mood in male patients with mild Alzheimer disease and healthy elderly men. Arch Neurol. 2006;63:177-185.
34. Gray PB, Singh AB, Woodhouse LJ, et al. Dose-dependent effects of testosterone on sexual function, mood, and visuospatial cognition in older men. J Clin Endocrinol Metab. 2005;90:3838-3846.
35. Katznelson L, Robinson MW, Coyle CL, et al. Effects of modest testosterone supplementation and exercise for 12 weeks on body composition and quality of life in elderly men. Eur J Endocrinol. 2006;155:867-875.
36. Sinha-Hikim I, Cornford M, Gaytan H, et al. Effects of testosterone supplementation on skeletal muscle fiber hypertrophy and satellite cells in community-dwelling older men. J Clin Endocrinol Metab. 2006;91:3024-3033.
37. Coviello AD, Kaplan B, Lakshman KM, et al. Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. J Clin Endocrinol Metab. 2008;93:914-919.
38. AndroGel [prescribing information]. Marietta, GA: Solvay Pharmaceuticals, Inc.; 2009.
39. Roddam AW, Allen NE, Appleby P, et al; for the Endogenous Sex Hormones and Prostate Cancer Collaborative Group. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. J Natl Cancer Inst. 2008;100:170-183.
40. Marks LS, Mazer NA, Mostaghel E, et al. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. JAMA. 2006;296:2351-2361.
41. American Urological Association Education and Research, Inc. Chapter 1: AUA guideline on the management of benign prostatic hyperplasia: Diagnosis and treatment recommendations. http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/bph-management/chapt_1_appendix.pdf. Accessed May 6, 2010.
42. Miner MM, Sadovsky R. Evolving issues in male hypogonadism: evaluation, management, and related comorbidities. Cleve Clin J Med. 2007;74(suppl 3):S38-S46.
43. US Food and Drug Administration. Orange Book: Approved drug products with therapeutic equivalence evaluations. http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm. Accessed April 5, 2010.
44. AndroDerm [prescribing information]. Corona, CA: Watson Pharma, Inc.; 2005.
45. Striant [prescribing information]. Livingston, NJ: Columbia Laboratories, Inc.; 2003.
46. Depo-Testosterone [prescribing information]. Kalamazoo, MI: Pharmacia & Upjohn Company; 2002.