TABLE 411-5 MONITORING MEN RECEIVING TESTOSTERONE THERAPY

1. Evaluate the patient 3–6 months after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects.
2. Monitor testosterone level 3–6 months after initiation of testosterone therapy:
   - Therapy should aim to raise serum testosterone level into the mid-normal range.
     - Injectable testosterone enanthate or cypionate: Measure serum testosterone level midway between injections. If testosterone is >700 ng/dL (24.5 nmol/L) or >400 ng/dL (14.1 nmol/L), adjust dose or frequency.
     - Transdermal patches: Assess testosterone level 3–12 h after application of the patch; adjust dose to achieve testosterone level in the mid-normal range.
     - Buccal testosterone bioadhesive tablet: Assess level immediately before or after application of fresh system.
     - Transdermal gels and solution: Assess testosterone level 2–8 h after patient has been on treatment for at least 2 weeks; adjust dose to achieve serum testosterone level in the mid-normal range.
     - Testosterone pellets: Measure testosterone levels at the end of the dosing interval. Adjust the number of pellets and/or the dosing interval to achieve serum testosterone levels in the normal range.
     - Oral testosterone undecanoate[a]: Monitor serum testosterone level 3–5 h 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 3–6 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; reinitiate therapy with a reduced dose.
4. Measure bone mineral density of lumbar spine and/or femoral neck after 1–2 years of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture, consistent with regional standard of care.
5. In men 40 years of age or older with baseline PSA >0.6 ng/mL, perform digital rectal examination and check PSA level before initiating treatment, at 3–6 months, and then in accordance with guidelines for prostate cancer screening depending on the age and race of the patient.
6. Obtain urologic consultation if there is:
   - An increase in serum PSA concentration >1.4 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 AUA/IPSS 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, cypionate, and undecanoate): Ask about fluctuations in mood or libido and, rarely, cough after injections.
   - 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 4–6 h after application of the testosterone gel.
   - Testosterone pellets: Look for signs of infection, fibrosis, or pellet extrusion.

[a]Not approved for clinical use in the United States.

Abbreviations: AUA/IPSS, American Urological Association/International Prostate Symptom Score; PSA, prostate-specific antigen.

Source: Reproduced with permission from the Endocrine Society Guideline for Testosterone Therapy of Androgen Deficiency Syndromes in Adult Men (S Bhasin et al: J Clin Endocrinol Metab 95:2536, 2010).

levels, due to increased erythropoiesis, suppression of hepcidin, and increased iron availability for erythropoiesis. The magnitude of hemoglobin increase during testosterone therapy is greater in older men than younger men and in men who have sleep apnea, a significant smoking history, or chronic obstructive lung disease. The frequency of erythrocytosis is higher in hypogonadal men treated with injectable testosterone esters than in those treated with transdermal formulations, presumably due to the higher testosterone dose delivered by the typical regimens of testosterone esters. Erythrocytosis is the most frequent adverse event reported in testosterone trials in middle-aged and older men and is also the most frequent cause of treatment discontinuation in these trials. If hematocrit rises above 54%, testosterone therapy should be stopped until hematocrit has fallen to <50%. After evaluation of the patient for hypoxia and sleep apnea, testosterone therapy may be reinitiated at a lower dose.

PROSTATE AND SERUM PROSTATE-SPECIFIC ANTIGEN LEVELS Testosterone replacement therapy increases prostate volume to the size seen in age-matched controls but does not increase prostate volume beyond that expected for age. There is no evidence that testosterone therapy causes prostate cancer. However, androgen administration can exacerbate preexisting metastatic prostate cancer. Many older men harbor microscopic foci of cancer in their prostates. It is not known whether long-term testosterone administration will induce these microscopic foci to grow into clinically significant cancers.

Prostate-specific antigen (PSA) levels are lower in testosterone-deficient men and are restored to normal after testosterone replacement. There is considerable test-retest variability in PSA measurements. Increments in PSA levels after testosterone supplementation in androgen-deficient men are generally <0.5 ng/mL, and increments >1.0 ng/mL over a 3- to 6-month period are unusual. The 90% confidence interval for the change in PSA values in men with benign prostatic hypertrophy, measured 3–6 months apart, is 1.4 ng/mL. Therefore, the Endocrine Society expert panel suggested that an increase in PSA >1.4 ng/mL in any 1 year after starting testosterone therapy, if confirmed, should lead to urologic evaluation. PSA velocity criterion can be used for patients who have sequential PSA measurements for >2 years; a change of >0.40 ng/mL per year merits closer urologic follow-up.

CARDIOVASCULAR RISK In epidemiologic studies, testosterone concentrations are negatively related to the risk of diabetes mellitus, heart disease, and all-cause and cardiovascular mortality. A recent testosterone trial in older men with mobility limitation was stopped early because of the higher rates of cardiovascular events in the testosterone arm than in the placebo arm of this trial. Meta-analyses