Aerospace Medicine Clinic

This article was prepared by Jeffrey Harris, M.D., M.O.H.

Would out the flight surgeon who receives a call from a 44-yr-old male U.S. Air Force pilot. He has recently moved into the area and is returning to an active flying job after a few years away. During the previous year he was started on testosterone therapy by a civilian medical provider. He did not follow up with the provider after initiating treatment. The patient reports improvement in his energy levels, mood, and libido since starting the therapy and is requesting a refill of the medication at the time of his flight physical.

You remember reading that testosterone replacement treatment (TRT) has become increasingly popular over the last few years, especially among military members, and that around 50% of military men on TRT did not meet the diagnostic criteria specified in consensus guidelines.^{7,8} You explain to the pilot you will need the clinical notes from the provider who started him on the treatment and that he will require a flying waiver before he can be cleared to return to flying.¹⁴ The Air Force Waiver Guide specifies that patients who do not meet the diagnostic criteria are "unlikely to receive a waiver"⁹ for continued use of exogenous testosterone. The pilot agrees to send in the medical records from the endocrinologist for your review prior to his office visit.

- 1. Which is true regarding the initial diagnosis of hypogonadism (testosterone deficiency)?
 - A. Definitive results on the Androgen Deficiency in the Aging Male questionnaire, or another of the validated testosterone deficiency questionnaires, can be considered diagnostic.
 - B. Starting at age 40, men should undergo routine screening for low testosterone.
 - C. Free testosterone levels are a more reliable indicator of disease than total testosterone.
 - D. In a patient with symptoms, a single total testosterone level is sufficient to make the diagnosis if it is drawn in the morning and the result is more than 20% below the normal value.
 - E. A recent upper respiratory illness, alcohol use, and food intake will all lower testosterone levels.

ANSWER/DISCUSSION

1. E. The American Urological Association (AUA) and the Endocrine Society each published consensus guidelines in 2018 regarding diagnosis and management of low testosterone levels.^{1,10} Both guidelines agree that the diagnosis should be made only in a patient with symptoms of low testosterone and at least two morning total testosterone levels below $300 \text{ ng} \cdot \text{dL}^{-1}$. The labs should be drawn during the normal diurnal spike between 08:00 and 10:00 with the patient fasting. Symptoms that are considered more specific to low testosterone include loss of libido, erectile dysfunction, gynecomastia, and osteoporosis.² Many of the other symptoms are nonspecific, such as decreased energy, depression, poor concentration, and loss of muscle mass.¹

There are no standardized questionnaires that are validated for use in making a definitive diagnosis.¹⁰ Only men who have clinical symptoms suggesting deficiency should be tested; there is no reason for routine screening, regardless of age.¹

Because the methods used to determine free testosterone may vary widely, its use is not routinely recommended in the AUA guidelines. The Endocrine Society does include a reliable, free testosterone value as a diagnostic criterion in certain clinical situations.¹ The majority of testosterone in the blood is bound to proteins, mainly albumin and sex hormone binding globulin (SHBG). In a patient with clinical symptoms of hypogonadism with borderline total testosterone levels, a physician may want to measure SHBG and free testosterone. Obesity, diabetes, use of glucocorticoids, and thyroid disorders are some of the more common reasons for abnormal SHBG levels.¹

A single measurement should not be used to make the diagnosis because up to 50% of patients with total testosterone levels below $300 \text{ ng} \cdot \text{dL}^{-1}$ will have normal levels on repeat testing.¹³ Several factors can temporarily lower hormone levels, including all those listed in response E. Individuals who

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have recently used opioids or glucocorticoids may have lower levels, as well as those who recently stopped using exogenous testosterone.¹

The pilot contacts your clinic once he has received the notes and lab results from his endocrinologist. He asks if there are specific labs other than testosterone levels that you will need to see.

- 2. Besides total testosterone, what other screening/diagnostic tests should have been included in the pretreatment workup for this patient with hypogonadism?
 - A. Hematocrit.
 - B. Prostate specific antigen (PSA).
 - C. Karyotype testing.
 - D. Follicle stimulating hormone (FSH) and luteinizing hormone (LH).
 - E. All of the above.

ANSWER/DISCUSSION

2. E. Hematocrit levels should be checked prior to initiating therapy in all patients. PSA levels are recommended prior to initiating TRT for patients over 40 yr of age. Karyotype testing would be useful to evaluate for Klinefelter syndrome, which, along with history of trauma and orchitis, is a common cause of primary hypogonadism.¹ Studies estimate that only around 25% of men with Klinefelter syndrome are diagnosed, and the mean age of diagnosis is in the mid-30s.⁶

FSH and LH levels should be checked to help differentiate primary hypogonadism from secondary causes. Both levels are expected to be elevated in a patient with a functioning hypothalamic pituitary axis, and normal or low levels should prompt an evaluation for secondary hypogonadism.² Several of the causes of secondary disease may also impact a flyer's medical clearance and require further workup when FSH/LH levels are lower than expected.

- 3. Which of the following is not an aeromedically significant condition that should be considered as a possible cause of secondary hypogonadism?
 - A. Pituitary tumor.
 - B. Head trauma.
 - C. Obstructive sleep apnea (OSA).
 - D. Hemochromatosis.
 - E. Hypothyroidism.

ANSWER/DISCUSSION

3. E. Disease processes that affect the hypothalamic pituitary axis will result in secondary hypogonadism. Each of the answers A–D are potential causes and each can significantly affect safety of flight beyond the symptoms of testosterone deficiency. Patients with hypopituitarism will present with both hypothyroidism and hypogonadism. While they are

sometimes associated, low testosterone is not caused by hypothyroidism; therefore, the correct answer is E.

When evaluating for secondary hypogonadism, a physician should consider potentially reversible causes of disease, such as nutritional deficiencies or obesity. A thorough history may reveal other potential causes, like significant head trauma or OSA. The provider should check prolactin levels and iron studies in all patients to exclude hyperprolactinemia and hemochromatosis. Patients with severe disease (total testosterone levels <150 ng \cdot dL⁻¹) or any neurological symptoms should be evaluated with magnetic resonance imaging to look for a tumor or infiltrative disease of the hypothalamus or pituitary gland.¹

The pilot brings in records from the endocrinologist documenting his pretreatment symptoms and lab results, which met diagnostic criteria in accordance with current guidelines. His FSH and LH levels were above normal, indicating primary hypogonadism. The exact cause of his testosterone deficiency is not known but is presumed to be a result of a viral orchitis he experienced several years previously. Your patient had no abnormalities in the screening labs from the previous provider. He has been using a topical testosterone preparation with good results in both symptom improvement and normalization of testosterone. You agree to continue the patient's current testosterone prescription.

Because he is using a testosterone gel, you counsel the patient to avoid transference of the medication from the gel to close contacts. You have a lengthy discussion with the patient explaining the significant risks and benefits of the medication.

- 4. Which of the following is an accurate statement about medication risks and benefits?
 - A. Patients receiving TRT have a much higher risk of developing prostate cancer.
 - B. Current evidence demonstrates TRT is associated with elevated risk of coronary artery disease.
 - C. The most common adverse effect reported in trials of TRT is erythrocytosis.
 - D. Properly dosed TRT improves OSA.
 - E. Testosterone therapy increases sperm production.

ANSWER/DISCUSSION

4. C. Erythrocytosis is a common adverse reaction and, for that reason, patients receiving TRT should have hematocrit monitored regularly.¹ Although the guidelines recommend checking a PSA prior to starting therapy in men over age 40, there is no evidence linking TRT to prostate cancer.⁴ Similarly, available evidence does not show an increase in cardiovascular events in men on TRT.¹² Patients with untreated severe OSA may experience a worsening of their apnea if started on TRT.¹ Because many symptoms of hypogonadism can be shared with OSA, providers should be diligent about considering the diagnosis of OSA and controlling apnea symptoms prior to initiating TRT. It is well documented that exogenous testosterone inhibits

spermatogenesis and should not be used in men interested in conceiving. 10

You check the medical standards references to determine what is needed to get this pilot approved to return to flying. For Air Force pilots, the diagnosis of hypogonadism and sustained use of hormone therapy are disqualifying.¹⁴ The Navy and the Army* also consider hypogonadism as disqualifying for flying duty.¹¹ All three services allow for a waiver in adequately treated aviators.*^{9,11} In civilian aviation, the Federal Aviation Administration does not consider testosterone replacement therapy as disqualifying for medical certification.⁵

Your patient is granted a waiver and has safely returned to flying status. You check his testosterone levels and hematocrit at 6 mo and again prior to his 1-yr follow-up. During his appointment you notice increased acne on his face and back. His labs show supratherapeutic testosterone levels and polycythemia with a hematocrit of 56%.

- 5. Which statement is correct regarding erythrocytosis/ polycythemia caused by exogenous testosterone therapy?
 - A. When compared to other causes of polycythemia, TRT carries a greater risk of venous thromboembolic events (VTE).
 - B. The patient should stop using testosterone until his labs normalize, then may be able to restart at a lower dose.
 - C. The patient can continue on the same dose of medication if he regularly donates blood.
 - D. The patient should be switched from the topical to the injectable form of the medication.

ANSWER/DISCUSSION

5. B. As this patient has both elevated hematocrit and elevated testosterone levels, he should stop taking the testosterone until his hematocrit normalizes. If he needs to restart the medication, it should be at a lower dose.¹

Polycythemia itself is a risk for VTE, but the role of TRT is not as clear. The Food and Drug Administration has required manufacturers to include a warning about VTE for TRT; however, studies looking at VTE have found conflicting results.¹ A recent study of U.S. veterans found current TRT patients did not have an increased risk of VTE.¹² The AUA recommends informing patients that there is not definitive evidence linking TRT with an increase in VTE.¹⁰

Using therapeutic phlebotomy could be an option for patients with polycythemia,³ but in this case the patient's testosterone levels were elevated, so his dose must also be adjusted. Testosterone injections carry a higher incidence of polycythemia than topical forms.¹ You advise the patient that he must discontinue the medication and bring him down off flight status until his symptoms and labs improve. You warn the patient that he is likely to experience a resurgence of testosterone deficiency symptoms, as he had grown accustomed to the exogenous steroid. You refer him to a local endocrinologist to assist in managing the withdrawal from the medication and determining when and how to restart TRT.

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