Frequently Asked Questions

1. Although hypogonadism is a highly prevalent condition, many hypogonadal men are not receiving testosterone therapy. What are the most significant obstacles to diagnosing hypogonadism and treating it with testosterone therapy?

For many men, symptoms of illness go undetected simply because they do not get routine checkups and preventive care.[1] Social taboos or embarrassment also can impede an open discussion about health concerns.[1] Because symptoms of hypogonadism so often are not reported by male patients, clinicians need to look for the signs and symptoms of hypogonadism to appropriately assess for and diagnose this condition.[2]

According to a Harris Interactive survey, up to 33% percent of men older than 39 years reported having experienced at least 2 symptoms of hypogonadism in the past year, however, 97% reported that they had never broached the subject of low testosterone with their physician.[3] The physician may initiate discussion and encourage communication to help a patient overcome feelings of embarrassment or discomfort when discussing his health concerns in general.[1] It is essential for the physician to continue a dialogue with the patient to uncover potential symptoms of hypogonadism.[2]

Because of the nonspecific nature of the signs and symptoms of hypogonadism, physicians may not recognize the clinical manifestations and the condition remains underdiagnosed.[4] However, as the benefits of testosterone therapy are increasingly recognized, the estimated 95% of American men with hypogonadism who currently remain untreated is expected to decrease.[4]

2. What are the most common presenting symptoms of male hypogonadism? How do you assess whether a man has hypogonadism?

Signs and symptoms of testosterone deficiency are vague and nonspecific and may vary based on age and comorbid conditions. Hypogonadism is characterized by the presence of low serum testosterone levels (<300 ng/dL) along with at least one clinical symptom[2,5]:

- Decreased sexual desire and sexual activity
- Fewer morning or spontaneous erections
- Gynecomastia
- Loss of body hair, less shaving
- Height loss, low trauma fracture, low bone mineral density
- Reduced muscle bulk and strength
- Hot flashes, sweats
- Lower energy and motivation
- Sadness, depressed mood
- Poor concentration and memory
- Sleep disturbance
- Increased body fat or body mass index (BMI)

© 2009 CogniMed Inc. All rights reserved.

Clinicians should consider whether serum testosterone evaluation is appropriate when patients present with the aforementioned signs and symptoms. The Endocrine Society guidelines suggest that diagnosing androgen deficiency in men should be based on the following criteria[5]:

- Diagnose androgen deficiency only in men with consistent signs and symptoms plus low serum testosterone levels
- Measure morning total testosterone as the initial diagnostic test
- Confirm low levels of total testosterone with repeat measurements
- Do not diagnose androgen deficiency during an acute or subacute illness

3. Which comorbid conditions warrant screening for male hypogonadism, and what are the effects of hypogonadism on those comorbid conditions (eg, cardiovascular disease (CVD), type 2 diabetes, osteoporosis, metabolic syndrome, obesity, sleep apnea, anemia, and sarcopenia). What are the common attributes of these comorbid conditions with respect to clinical presentation and symptomatology?

Low testosterone levels are associated with an array of chronic comorbidities, including obesity, metabolic syndrome, diabetes mellitus, hypertension, CVD, depressed mood, prostate disease, decreased cognitive function, erectile dysfunction (ED),[6-8] and sleep apnea.[9,10]

According to the Endocrine Society Guidelines, a man should be screened for hypogonadism if he presents with any of the following[5]:

- Sellar mass or radiation to or diseases of the sellar region
- Medications that affect testosterone production or metabolism (eg, opioids, glucocorticoids, and ketoconazole)
- Human immunodeficiency virus-associated weight loss
- End-stage renal disease and maintenance hemodialysis
- Moderate to severe chronic obstructive lung disease
- Infertility
- Osteoporosis or a low-trauma fracture, especially in a young man
- Type 2 diabetes

Additionally, clinicians should consider the following when determining whether screening for hypogonadism is warranted:

- Low serum testosterone levels may predispose patients to visceral adiposity; furthermore, visceral adiposity suppresses testosterone production[6]
- Low total testosterone levels may be predictive of the development of diabetes and metabolic syndrome in middle-aged men; therefore, hypgonadism may be considered an early marker for altered insulin and glucose metabolism[6,11,12]
- A higher risk of metabolic syndrome is associated with low testosterone, especially in middle-aged men with a BMI <25.[13] Androgen deficiency may be an early marker for cardiovascular risk, because nonobese men with low total

© 2009 CogniMed Inc. All rights reserved.

testosterone were at 2- to 4-fold greater risk for metabolic syndrome during 15 years of follow-up[13]
    - If hypogonadism in middle-aged men is predictive of metabolic syndrome developing later in life, screening for hypogonadism and treating it with testosoterone therapy may prevent metabolic syndrome or slow or halt its progression to diabetes and CVD[14]
- Hypogonadism and idiopathic depression share common symptoms, including decreased libido, fatigue, and changes in affect.[8] Bioavailable testosterone levels decrease with age to a much greater extent than total testosterone levels and can drop by as much as 40% between the ages of 40 and 70.[15] Because old age is also associated with an increased prevalence of depressed mood, the association of testosterone and mood has been studied in hypogonadal men.[15] Bioavailable testosterone levels were significantly lower (by 17%) in men with clinically defined depression compared to levels observed in other men.[15] Consequently, testosterone treatment may improve depressed mood in older men who have low levels of bioavailable testosterone.[15] Furthermore, testosterone therapy has been shown to rapidly improve and maintain mood parameters throughout treatment[16]

4. In patients with concomitant hypogonadism and ED, what are the benefits of prescribing testosterone therapy in combination with other ED treatments?

Suppression of testosterone in men leads to reduced sexual desire and activity and may result in ED.[17] Low serum testosterone correlates with impaired cavernous vasodilatation in men with ED; for men who are nonresponsive to phosphodiesterase type 5 (PDE5) inhibitor monotherapy for ED, testosterone therapy may be considered as a concomitant therapy.[18] Studies show that testosterone therapy as an adjunct to PDE5 inhibitor therapy may improve erectile function for hypogonadal men with ED and low testosterone levels who did not respond to PDE5 inhibitor monotherapy.[17,18] Furthermore, studies show that using testosterone therapy to achieve eugonadal serum testosterone levels improves libido.[19]

5. Is hypogonadism considered a predictive marker for CVD and mortality risk?

High endogenous testosterone concentrations are associated with a favorable CVD risk profile (eg, increased high-density lipoprotein concentrations, lower blood pressure, and decreased serum triglyceride and glucose levels). A growing body of evidence indicates that endogenous testosterone levels are inversely related to mortality due to CVD and, consequently, low testosterone may be a predictive marker for patients at high risk for CVD.[20]

Khaw and colleagues studied the relationship between endogenous testosterone levels and mortality by examining mortality due to all causes, including CVD and cancer, in a nested case-control study of 11,606 men.[20] After excluding deaths that occurred in the first 2 years, inverse relationships were observed for deaths due to cardiovascular causes.

© 2009 CogniMed Inc. All rights reserved.

In addition, Laughlin et al examined the association of endogenous testosterone concentrations with mortality in a prospective study of 794 men (mean follow-up, 11.8 y).[21] Independent of age, lifestyle, and adiposity, men with low testosterone concentrations were shown to have a 40% higher mortality risk over a 20-year period compared to men with normal testosterone.

Randomized placebo-controlled trials examining the effect of exogenous testosterone therapy on duration and quality of life are warranted.[21]

6. What effect does testosterone therapy have on the risk of prostate cancer occurrence or progression?

Use of testosterone therapy to treat hypogonadism may be constrained by longstanding concerns about safety.[20] Despite historical apprehension based on Huggins and Hodges' landmark observation that testosterone reduction causes regression of metastatic prostate cancer and that testosterone administration promotes growth of metastatic prostate cancer,[22] a growing body of evidence indicates that testosterone therapy is not associated with prostate cancer occurrence or progression.[4,9] Preliminary studies indicate that exogenous testosterone therapy does not increase prostate cancer risk regardless of history of prostate cancer.[23-25] Recent studies have shown that testosterone therapy may restore serum testosterone levels to eugonadal levels without adversely affecting the prostate.[25] Careful monitoring for evidence of prostatic disease is essential for patients undergoing testosterone therapy.[4,23,25] For more detailed discussion, click here.

7. Is it safe to treat hypogonadal men with exogenous testosterone therapy after curative radical prostatectomy or brachytherapy for localized prostate cancer?

Although testosterone therapy for patients with a history of prostate cancer has traditionally been contraindicated, a few studies have explored whether patients may be treated safely and efficaciously with testosterone therapy after curative treatment for prostate cancer:

- In a retrospective case analysis of 7 men with eugonadal serum testosterone levels before curative radical prostatectomy for prostate cancer, Kaufman et al demonstrated that patients with clinical signs of hypogonadism and low serum testosterone levels and who had received testosterone therapy for 1 to 12 years had no local recurrence or metastasis of prostate cancer during follow-up.[26] Monitoring of prostate-specific antigen (PSA) levels and clinical courses was regularly conducted after testosterone therapy was initiated
- Sarosdy evaluated hypogonadal patients receiving testosterone therapy (0.5 to 8.5 y; median, 4.5 y) after brachytherapy treatment for early-stage prostate cancer in a cohort of 31 men.[27] Total testosterone levels increased from a median of 188 ng/dL to 498 ng/dL after testosterone therapy initiation. No patient discontinued testosterone therapy because of prostate cancer recurrence or progression, suggesting that selected patients who have been treated

© 2009 CogniMed Inc. All rights reserved.

successfully for early-stage, localized prostate cancer may be safely treated with testosterone therapy

Well-designed, large-scale, prospective clinical trials are necessary to clearly determine whether prostate health is affected by testosterone therapy.

8. How do the differentiating properties (ie, duration of action and mode of administration) of testosterone therapy formulations impart benefits or drawbacks, specifically with regard to patient well-being and disruption of lifestyle?

Testosterone therapy is recommended for symptomatic men with low testosterone levels to maintain or improve overall health, including muscle mass and strength, bone mineral density, sense of well-being, and sexual function.[5] Efficacy, safety, tolerability, pharmacokinetic profile, and the patient's lifestyle should be considered when determining which testosterone formulation best meets the patient's needs.

A variety of injectable, topical, and oral testosterone formulations are available or in development:

- Testosterone cypionate and testosterone enanthate are available for intramuscular injection. The dosage of either testosterone cypionate or testosterone enanthate for hypogonadal men is 50 to 200 mg administered every 2 weeks[28,29]
  - Testosterone cypionate or enanthate may cause fluctuations in mood or libido and excessive erythrocytosis, particularly for older patients[5]
  - Intramuscular injections may cause pain at the injection site[5]
- Testosterone undecanoate for intramuscular injection is a novel, long-acting formulation in development in the United States. The proposed dosing schedule is injection of 750 mg as an initial dose, at 4 weeks, and every 10 weeks thereafter[30]
  - Intramuscular injections may cause pain at the injection site[5]
- Testosterone pellets are implanted in minor outpatient surgical procedures. Four 200-mg pellets are implanted under the skin of the lateral abdominal wall or the buttocks, according to patient preference. Depending on individual patient characteristics, the pellets are effective for 5 to 7 months[31]
  - With testosterone pellets, there is a risk of expulsion, and the implant procedure carries the risk of infection[5]
- Topical testosterone gel is available in nonaerosol metered-dose pumps and unit-dose aluminum foil packets. The recommended starting dose is 5 g/day, which can be increased to 7.5 g and 10 g as needed to achieve testosterone concentrations in the normal range[32,33]
  - With topical testosterone gel comes the potential for transference from the patient to others. The patient should cover the application site with clothing and wash skin and hands with soap before having skin-to-skin contact[5]
- The transdermal patch system provides continuous delivery of testosterone for 24 hours after application to intact, nonscrotal skin (eg, back, abdomen, thighs,

© 2009 CogniMed Inc. All rights reserved.

upper arms). The usual starting dose is one 5-mg patch or two 2.5-mg patches applied nightly for 24 hours, providing a total dose of 5 mg/day. Serum testosterone concentrations outside the normal range may require increasing the daily dose to 7.5 mg (ie, one 5-mg plus one 2.5-mg patch or three 2.5-mg patches) or decreasing the daily dose to 2.5 mg (ie, one 2.5-mg patch), maintaining nightly application[34]
    - Testosterone transdermal patches may cause skin irritation at the application site[5]
- The testosterone buccal system adheres to the gum or inner cheek and releases a controlled, sustained amount of testosterone through the buccal mucosa as the system gradually hydrates. One system, containing 30 mg testosterone, is inserted twice daily[35]
    - The testosterone buccal system may alter taste and irritate gums[5]

The ideal testosterone formulation for hypogonadism would produce physiologic levels of testosterone for prolonged periods and have a favorable safety profile.[36] The dosing schedule and administration method would be convenient for the patient. Ideally, the formulation would be reasonably priced.

9. When treating male patients for hypogonadism, which parameters should define treatment efficacy and success (eg, signs and symptoms, serum testosterone concentrations)?

There is no consensus regarding target levels of testosterone therapy, although aiming for the mid- to upper-normal range optimizes the response to treatment.[37] If an adequate clinical response to testosterone therapy is reported by the patient (eg, alleviation of signs and symptoms), dose titration may be considered unnecessary, even if serum testosterone levels are in the low-normal range.[37] Switching to intramuscular testosterone therapy should be considered if the maximum recommended dose of transdermal therapy does not sufficiently elevate serum testosterone levels.[37]

10. For testosterone therapy, which specific monitoring steps (eg, laboratory evaluation, physical examination) must be included in a comprehensive evaluation to optimize patient health (ie, pre- and post-treatment digital rectal examination (DRE); sleep apnea assessment; voiding symptom evaluation; serum evaluation of testosterone, PSA, hematocrit, and hemoglobin levels; and biopsy, when applicable)?

Once testosterone therapy is initiated, a follow-up visit in 1 to 2 months is recommended to assess the efficacy of treatment compared to the baseline evaluation.[4,37] Dosage adjustment may be needed if treatment response has been suboptimal.[37] Monitoring visits should occur at 3- to 6-month intervals for the first year, followed by yearly assessments.[37] Symptoms should be evaluated at each visit, including urinary symptoms, gynecomastia, or sleep apnea.[37] A DRE should be performed, as well as blood tests to measure serum testosterone, PSA, and hematocrit.[37] A prostate biopsy should be

© 2009 CogniMed Inc. All rights reserved.

conducted if there is a significant increase in PSA or a change is observed from the DRE.[4,5,37]

11. Considering the chronic nature of hypogonadism and the imperativeness of regular testosterone therapy administration and monitoring, what information is critically important for clinicians to disseminate to patients?

Because the underlying conditions causing hypogonadism are irreversible, consistent, long-term testosterone therapy is necessary.[38] Studies determining the impact of acute sex steroid withdrawal have demonstrated a significant reduction in insulin sensitivity prior to any detectable changes in body composition.[39] In addition, the beneficial effect of testosterone on metabolic syndrome is likely related to its impact on body composition, which occurs with long-term (6-12 months) administration.[6] Low testosterone levels in hypogonadal men also lead to high bone loss and the consequent increased risk of osteoporotic fracture.[40] With respect to erectile function, testosterone therapy may be required for up to 24 weeks to restore anatomical and physiologic impairments.[19]

Because testosterone therapy is a long-term, chronic therapy, patient adherence is critical.[41] Adherence to therapy is more likely achieved when the patient is involved in the decision about the testosterone preparation and when administration is convenient.[38] The main goals of testosterone therapy are to achieve eugonadal testosterone levels and decrease symptoms and health risks associated with low testosterone levels.[5,41] Clinicians should consider the importance of educating patients about the following:

- Lack of adherence to a testosterone therapy regimen will result in fluctuating levels of plasma testosterone, which will not be maintained consistently in the normal range[41]
- Nonadherence may lead to impaired sexual function, reduced muscle and bone mass, and lower quality of life due to worsened mood and reduced vitality[41]
- Even a short duration of hypogonadism can affect insulin sensitivity independent of apparent alterations in body fat composition[39]

© 2009 CogniMed Inc. All rights reserved.

References

1. Sandman D, Simantov E, An C. Out of touch: American men and the health care system. http://www.cmwf.org. Accessed December 15, 2008. Publication no. 374.
2. Seftel A. Male hypogonadism, II: etiology, pathophysiology, and diagnosis [review]. *Int J Impot Res.* 2006;18(3):223-228.
3. Alliance for Aging Research. Low testosterone: men's health condition in the shadows. http://www.agingresearch.org/content/article/detail/714/. Accessed March 25, 2009.
4. Dobs AS, Morgentaler A. Does testosterone therapy increase the risk of prostate cancer [review]? *Endocr Pract.* 2008;14(7):904-911.
5. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2006;91(6):1995-2010.
6. Shabsigh R, Arver S, Channer KS, et al. The triad of erectile dysfunction, hypogonadism and the metabolic syndrome [review]. *Int J Clin Pract.* 2008;62(5):791-798.
7. Makhlouf AA, Mohamed MA, Seftel AD, Niederberger C. Hypogonadism is associated with overt depression symptoms in men with erectile dysfunction. *Int J Impot Res.* 2008;20(2):157-161.
8. Kshirsagar A, Seftel A, Ross L, Mohamed M, Niederberger C. Predicting hypogonadism in men based upon age, presence of erectile dysfunction, and depression. *Int J Impot Res*. 2006;18(1):47-51.
9. Gooren L. Androgen deficiency in the aging male: benefits and risks of androgen supplementation. *J Steroid Biochem Mol Biol.* 2003;85(2-5):349-355.
10. Mulligan T, Frick MF, Zuraw QC, Stemhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int J Clin Pract*. 2006;60(7):762-769.
11. Laaksonen DE, Niskanen L, Punnonen K, et al. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care.* 2004;27(5):1036-1041.
12. Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. *Eur J Endocrinol.* 2006;154(6):899-906.
13. Kupelian V, Page ST, Araujo AB, Travison TG, Bremner WJ, McKinlay JB. Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the metabolic syndrome in nonobese men. *J Clin Endocrinol Metab*. 2006;91(3):843-850.
14. Makhsida N, Shah J, Yan G, Fisch H, Shabsigh R. Hypogonadism and metabolic syndrome: implications for testosterone therapy. *J Urol*. 2005;174(3):827-834.
15. Barrett-Connor E, Von Mühlen DG, Kritz-Silverstein D. Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo study. *J Clin Endocrinol Metab*. 1999;84(2):573-577.
16. 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

© 2009 CogniMed Inc. All rights reserved.

mass, and bone mineral density in hypogonadal men. *J Clin Endocrinol Metab.* 2004;89(5):2085-2098.

17. Shabsigh R. Testosterone therapy in erectile dysfunction. *Aging Male.* 2004;7(4):312-318.
18. Shabsigh R, Kaufman JM, Steidle C, Padma-Nathan H. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *J Urol.* 2008;179(5 suppl):S97-S102.
19. Yassin AA, Saad F. Improvement of sexual function in men with late-onset hypogonadism treated with testosterone only. *J Sex Med*. 2007;4(2):497-501.
20. Khaw KT, Dowsett M, Folkerd E, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European Prospective Investigation Into Cancer in Norfolk (EPIC-Norfolk) prospective population study. *Circulation.* 2007;116(23):2694-2701.
21. Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. *J Clin Endocrinol Metab.* 2008;93(1):68-75.
22. Huggins C, Hodges CV. Studies on prostatic cancer, I: the effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res.* 1941;1:293-297. Reprinted by: *J Urol.* 2002;167(2, pt 2):948-951.
23. Morgentaler A. Testosterone replacement therapy and prostate cancer. *Urol Clin North Am*. 2007;34(4):555-563.
24. Shabsigh R, Crawford ED, Nehra A, Slawin KM. Testosterone therapy in hypogonadal men and potential prostate cancer risk: a systematic review [review]. *Int J Impot Res*. 2009;21(1):9-23.
25. Holyoak JD, Crawford ED, Meacham RB. Testosterone and the prostate: implications for the treatment of hypogonadal men. *Curr Urol Rep*. 2008;9(6):500-505.
26. Kaufman JM, Graydon RJ. Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men [review]. *J Urol*. 2004;172(3):920-922.
27. Sarosdy MF. Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. *Cancer*. 2007;109(3):536-541.
28. Delatestryl [package insert]. Lexington, MA: Indevus Pharmaceuticals Inc; 2005.
29. Depo-Testosterone [package insert]. Kalamazoo, MI: Pharmacia Corporation; 2002.
30. Morgentaler A, Dobs AS, Kaufman JM, et al. Long acting testosterone undecanoate therapy in men with hypogonadism: results of a pharmacokinetic clinical study. *J Urol.* 2008;180(6):2307-2313.
31. Testopel [package insert]. Rye, NY: Bartor Pharmacal Co Inc; 1992.
32. AndroGel [package insert]. Marietta, GA: Solvay Pharmaceuticals Inc; 2007.
33. Testim [package insert]. Malvern, PA: Auxilium Pharmaceuticals Inc; 2006.
34. Androderm [package insert]. Corona, CA: Watson Pharma Inc; 2007.
35. Striant [package insert]. Livingston, NJ: Columbia Laboratories Inc; 2003.

© 2009 CogniMed Inc. All rights reserved.

36. Edelstein D, Dobs A, Basaria S. Emerging drugs for hypogonadism [review]. *Expert Opin Emerging Drugs.* 2006;11(4):685-707.
37. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring [review]. *N Engl J Med.* 2004;350(5):482-492.
38. Gooren LJ. New long-acting androgens. *World J Urol*. 2003;21(5):306-310.
39. Yialamas MA, Dwyer AA, Hanley E, Lee H, Pitteloud N, Hayes FJ. Acute sex steroid withdrawal reduces insulin sensitivity in healthy men with idiopathic hypogonadotropic hypogonadism. *J Clin Endocrinol Metab*. 2007;92(11):4254-4259.
40. Lee H, Finkelstein JS, Miller M, Comeaux SJ, Cohen RI, Leder BZ. Effects of selective testosterone and estradiol withdrawal on skeletal sensitivity to parathyroid hormone in men. *J Clin Endocrinol Metab*. 2006;91(3):1069-1075.
41. Gooren LJ, Bunck MC. Androgen replacement therapy: present and future. *Drugs.* 2004;64(17):1861-1891.

For additional information on hypogonadism and its treatment, please visit
www.TestosteroneUpdate.org

© 2009 CogniMed Inc. All rights reserved.