American Urological Association

Conference Courier Highlights Report on Hypogonadism

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Hypogonadism has an important impact on men's overall health and well-being. This topic was the focus of one course (Course 771C, *Hypogonadism and Testosterone Replacement Therapy in Current Urologic Practice*) given at the annual meeting of the American Urological Association (AUA) held May 28 to June 3, 2010, in San Francisco, California. The course was presented by 3 acknowledged experts in the field: Wayne J.G. Hellstrom, MD; Darius A. Paduch, MD, PhD; and Craig F. Donatucci, MD.

Hypogonadism and its management were also addressed as part of two other courses ("Male Hypogonadism: Impact on Men's Health," presented by Allen D. Seftel, MD, in Course 019PG, *Urologic Diseases for the Allied Health Professional*, and "Testosterone Pellet (Testopel) Insertion," presented by Mohit Khera, MD, in Course 112HO, *Hands-on Office Treatment of Male Sexual Dysfunction*), and original research in the field was presented at Podium Session 43, *Sexual Function/Dysfunction/Andrology: Medical and Nonsurgical Therapy II*.

The purpose of this Conference Courier is to briefly review some of the basic information and the newest data on hypogonadism and its management as presented at AUA 2010.

Hypogonadism and Its Impact on Men's Health

Testosterone is the primary androgenic hormone involved in the normal growth and development of male sex organs and the maintenance of secondary sex characteristics but also has other widespread physiologic effects, including development of bone and muscle.[1]

Hypogonadism is a clinical and biochemical syndrome characterized by typical symptoms (Table 1) and a consistent deficiency in testosterone levels resulting from disruption of one or more levels of the hypothalamic-pituitary-gonadal (HPG) axis.[3-5] Treatment is not recommended for asymptomatic men with low testosterone levels.[3-5] Many of the symptoms of hypogonadism are subtle and nonspecific, developing slowly, and may be misinterpreted as the normal result of aging.

Hypogonadism is classified as primary (hypergonadotropic) or secondary (hypogonadotropic).[1] Primary hypogonadism is caused by abnormalities of the HPG axis at the testicular level; secondary hypogonadism is caused by central defects of the hypothalamus or pituitary gland.[4] Clinical hypogonadism is often of mixed etiology resulting from both reduced pulsatility of gonadotropins and decreased Leydig cell response. A number of drugs may cause or exacerbate hypogonadism. Physicians must be particularly aware,

Table 1. Signs and Symptoms of Hypogonadism[2-4]

PREPUBERTAL	POSTPUBERTAL[a]
Small testes, phallus, and prostate	Progressive decrease in muscle mass
Scant pubic and axillary hair	Increase in visceral fat
Disproportionately long arms and legs (from delayed epiphyseal closure)	Loss of libido
Reduced male musculature	Reduced erectile quality and frequency, including nocturnal erections
Gynecomastia	Oligospermia or azoospermia
Persistently high-pitched voice	Occasionally, menopausal-type hot flushes[b]
	Sleep disturbances
	Poor concentration, memory
	Decreased bone mineral density; osteopenia, osteoporosis
	Depressed mood, dysthymia
	Decreased energy, motivation, initiative, aggressiveness, and self-confidence
	Mild anemia (normochromic, normocytic; in the female range)

[a]Late-onset hypogonadism.
[b]Acute-onset hypogonadism.

because chronic pain is so widespread, that testosterone will be at castrate levels in patients taking opiates.[6]

Prevalent among men 45 years of age or older, hypogonadism (total testosterone [TT] <300 ng/dL) occurs in 30% to 40% of men visiting primary care physicians.[7] Approximately 4 to 5 million men in the United States are estimated to be hypogonadal,[8] but only about 5% of those are being treated.[1] Hypogonadism is found with increased prevalence in men who have certain comorbidities, particularly hypertension, diabetes, and obesity,[7,9] and has been linked to depression[10,11] and erectile dysfunction (ED). Recent data indicate that the prevalence of hypogonadism in men with ED peaks between 40 and 60 years of age and correlates strongly with work stress and sleep apnea.[12]

Loss of bone mineral density (BMD) with osteopenia and osteoporosis has been associated with hypogonadism, and bone fractures have been shown to increase among aging males.[13] Benito et al showed that deterioration of trabecular architecture in hypogonadal men was greater than that suggested by bone densitometry of the hip and spine.[14]

Low serum testosterone levels (<250 ng/dL or 8.7 nmol/L) have been associated with a higher all-cause mortality rate[15-17] and a higher risk of death from cardiovascular disease (CVD) and cancer, but not from respiratory diseases or other causes.[15] Low endogenous serum testosterone levels have been associated with increased risk of atherosclerosis of the abdominal aorta,[18] lower-extremity peripheral artery disease,[19] and coronary artery disease.[20] Castrate testosterone levels resulting from androgen suppression therapy have been associated with stiffening of the arteries,[21] the frequency and timing of myocardial infarctions (MIs),[22] an increased risk of incident diabetes and cardiovascular (CV) events,[23] and an increased risk of death from CV causes.[24,25] Low testosterone levels have been hailed as a potential marker for CVD. Although this concept is somewhat controversial, the data are sufficiently suggestive that patients should be referred to an internist for further evaluation and discussion of lifestyle changes.

Evaluation and Diagnosis

The field is challenging: Diagnosis of hypogonadism can be difficult and may require both the art and science of medicine.[26] The signs and symptoms of hypogonadism, as previously noted, are largely nonspecific. The hallmark of low testosterone is reduced libido and, in men with ED and testicular atrophy on physical examination, is highly specific for hypogonadism.[26] Focusing on these signs alone, however, will mean 40% to 50% of hypogonadal men who could benefit from treatment will be missed.[27] The use of a simple questionnaire that can be filled out in the waiting room will help to identify men who may need further evaluation.[28,29]

Hypogonadism is “a moving target”[30] with respect to testosterone levels, which vary according to laboratory, type of testing, and assay used and are complicated by the scarcity of reference ranges based on normal healthy men.[31] In addition, most of the reference ranges and recommendations for treatment are based on studies of older men—not men between 18 and 65 years of age—and many longitudinal studies did not stratify men according to sexual function.[31] Finally, it has been proposed that some men may be hypogonadal with varying degrees of androgen resistance and symptomatology.[32]

Nevertheless, some consensus exists: During hormonal treatment for prostate cancer, the castrate level of serum testosterone is <30 ng/dL; "true hypogonadism" in men who are not receiving androgen deprivation therapy is defined by a serum testosterone level <150 to 200 ng/dL, and such men will nearly always be symptomatic. The US Food and Drug Administration (FDA) arbitrarily defines hypogonadism, for purposes of product indications, as <300 ng/dL. In practice, however, testosterone levels from about 200 to 346 ng/dL are a "gray zone."[30] According to recent guidelines for the evaluation, diagnosis, and treatment of late-onset hypogonadism in men published by a joint panel from several professional societies, patients with serum TT levels of 230 ng/dL (<8 nmol/L) will usually benefit from treatment; TT levels between 230 and 350 ng/dL (8-12 nmol/L) warrant follow-up and repeat measurement of TT with sex hormone-binding globulin (SHBG) to calculate free testosterone (FT) or direct measurement of FT by equilibrium dialysis; and TT levels above 350 ng/dL (12 nmol/L) do not require treatment.[5,26,30]

Only 1% to 2% of the total serum testosterone is free or unbound; approximately half is tightly bound to SHBG, and the remainder is loosely bound to albumin.[26] Bioavailable testosterone (bioT) includes the free and albumin-bound portions; testosterone bound to SHBG is not functionally available to cells. TT levels are affected by levels of SHBG, which can vary widely and are influenced by age, illness, and medications.[4] For example, SHBG levels tend to be low in obesity, which drives down TT levels, although the bioavailable fraction may be normal. Levels of SHBG increase with age; older men may have normal levels of TT but be functionally hypogonadal.[26] Thus, testing for TT may not be informative for all men. Most laboratories will offer testing for both TT and FT. The most accurate method of measuring FT is direct testing by equilibrium dialysis; calculation of FT based on accurate levels of TT, SHBG, and serum albumin is acceptable.[26] Reference values may vary widely between different laboratories and assays; physicians should know the tests used by their local laboratory and use the lower limit of normal testosterone established by that laboratory.

In a recent study, first presented in Course 77IC at AUA 2010, Paduch et al found that healthy men with normal sexual function have much higher TT and FT levels than commonly reported as "normal" by commercial laboratories.[31] These results suggest that many men with sexual dysfunction who may benefit from testosterone therapy are never diagnosed with hypogonadism. This study emphasizes the importance of careful attention to signs and symptoms, particularly in men with testosterone levels in the low-normal range.

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels distinguish primary and secondary hypogonadism[4,5] (Table 2). Serum prolactin is indicated when TT is less than 150 ng/100 mL. Dr Seftel also recommended testing prolactin levels before initiating therapy because, if prolactin levels are elevated, testosterone therapy will not work; therefore, prolactin levels must be normalized before prescribing testosterone.[2] We usually recommend checking the serum prolactin when the testosterone level is low (<300 ng/dL) and the LH level is low or outside the normal range (G. R. Cunningham, written communication, July 2010).

Because of the normal diurnal variation in endogenous testosterone levels, with the highest levels occurring in early morning, the guidelines recommend that samples for testosterone testing be drawn in the morning,[2] although some experts suggest that blood should be drawn no later than 9:00 AM.[26] Fasting is not required. Purists recommend two samples, but other experts believe one is sufficient. The diurnal variation in testosterone levels is muted or absent in older men, with little variation throughout the day; therefore, time of the blood draw may be less important

in this age group.[33-35] Based on data from the Hypogonadism in Males (HIM) study, however, an early-morning blood draw may be preferable for any man younger than 75 years. The study assessed the effect of draw time (8:00-10:00 AM vs 10:00 AM-12:00 PM) on biochemical parameters. Levels of TT, FT, bioT, and SHBG did not differ significantly among men 75 years of age and older, and TT did not differ among men 45 years of age and older, but FT and bioT levels were higher at the earlier draw time.[36]

The physical examination of men with suspected hypogonadism should include a comprehensive history; evaluation for gynecomastia and secondary sexual characteristics (eg, body hair, beard growth); body mass index calculation; a testicular examination, noting size and consistency compared with approximate ranges of normal adult testes; and a prostate assessment, noting palpability.[2] Evaluation of prostate health, usually performed by internists, consists of a digital rectal examination (DRE) and prostate-specific antigen (PSA) test.

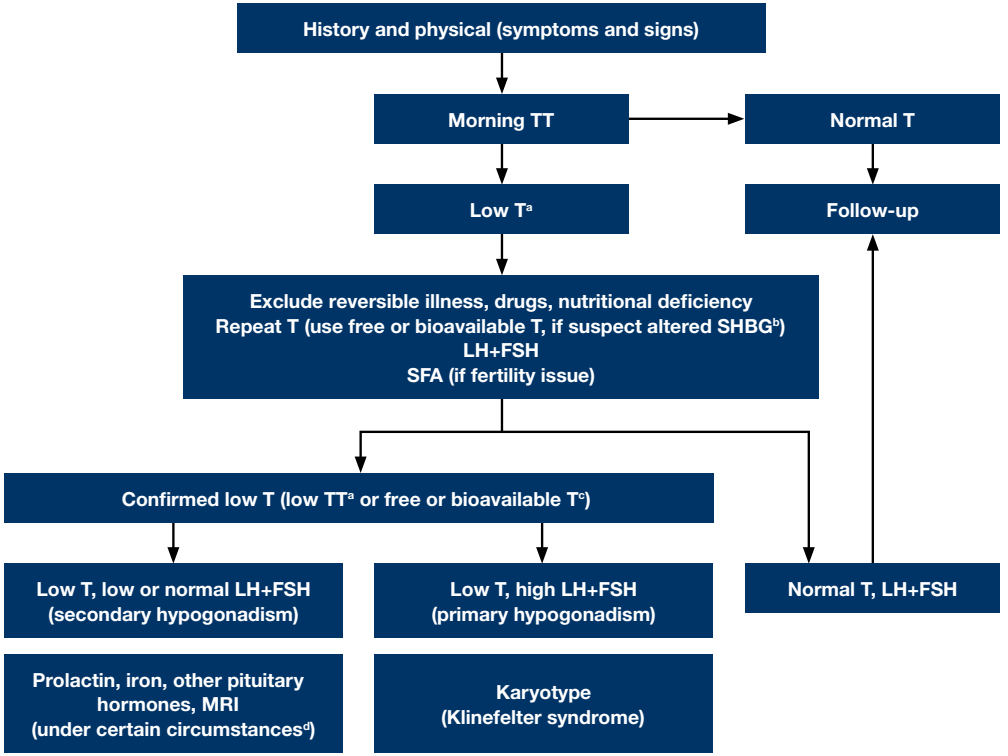
The recently published Endocrine Society clinical practice guideline provides a useful algorithm for the diagnostic evaluation of men with suspected hypogonadism[4] (Figure 1).

Table 2. Characteristics and Causes of Hypogonadism

PRIMARY	SECONDARY
Hypergonadotropic: ↓T, ↑LH, FSH	Hypogonadotropic: ↓T, ↓ or normal LH, FSH
Klinefelter syndrome	Acquired idiopathic
Mumps orchitis	Pituitary tumor
Autoimmune orchitis	Uremia
Trauma	Systemic illness
Testicular irradiation or surgery	Cranial irradiation
	Hyperprolactinemia
	Hemochromatosis
	Cushing syndrome
	Cirrhosis
	Morbid obesity
	Metabolic syndrome
	Type 2 diabetes

FSH, follicle-stimulating hormone; LH, luteinizing hormone; T, testosterone.

Figure 1. An approach for the diagnostic evaluation of adult men suspected of having androgen deficiency.



[a]LLN T range in healthy young men may vary in different laboratories. Physicians should use the LLN established by their reference laboratory.
[b]Refer to AACE guidelines, table 2, for conditions that alter SHBG concentrations.[2]
[c]LLN free T range may vary in different laboratories. Physicians should use the LLN established by their reference laboratory.
[d]Perform pituitary imaging to exclude pituitary and/or hypothalamic tumor or infiltrative disease if severe secondary hypogonadism is present (serum T <150 ng/dL, panhypopituitarism, persistent hyperprolactinemia, or signs or symptoms of tumor mass effect, such as headache, visual impairment, or visual field defect).

AACE, American Association of Clinical Endocrinologists; FSH, follicle-stimulating hormone; LH, luteinizing hormone; LLN, lower limit of normal; MRI, magnetic resonance imaging; SFA, seminal fluid analysis; SHBG, sex hormone-binding globulin; T, testosterone; TT, total testosterone.

Adapted with permission.[4]

Testosterone Therapy

The development of pharmacotherapy for hypogonadism is based on the science of androgenic hormones.[37] The two types of hormones important in human reproduction are peptides (gonadotropin-releasing hormone [GnRH], LH, and FSH) and steroids (testosterone, dihydrotestosterone [DHT], and estradiol [E_2]). GnRH stimulates the release of FSH and LH into the bloodstream.[37] During puberty, FSH binds to Sertoli cells, initiating spermatogenesis, which can then be sustained with human chorionic gonadotropin; LH binds to Leydig cells initiating the production of testosterone. Testosterone directly inhibits release of LH from the pituitary and indirectly inhibits release of GnRH via conversion to DHT and E_2. The balance between testosterone, DHT, and E_2 is critical. High levels of circulating E_2 may reduce the responsiveness of the pituitary gland to GnRH stimulation and release of FSH. In contrast, reducing production of E_2 (eg, by selective estrogen receptor modulators [SERMs] and aromatase inhibitors [AIs]) leads to an increase in the release of LH and FSH.

Sertoli cells also produce inhibin and activin, which inhibit and stimulate FSH release, respectively.[37] Inhibin B suppresses FSH release, and levels of inhibin B correlate positively with testicular volume and sperm count.[37,38] Responsiveness of gonadotrophs to GnRH is inhibited by prolactin, and elevated prolactin levels are a well-documented cause of hypogonadism. Discovery of the GPR54 receptor and the KiSS-1 gene product and their role in regulating the release of GnRH presents new targets for therapy for hypogonadism.[37] Circulating oxytocin has been implicated in control of Leydig cell function[39] and was recently correlated with testosterone levels.[37] Thus, regulation of testosterone levels is complex, and new discoveries in the physiology of the HPG axis will drive the development of new therapies.

Although growing evidence suggests that some of the actions of testosterone occur directly through membrane-bound receptors, the clinical effects of testosterone occur primarily through activation of transcription, which depends on binding to the androgen receptor (AR) in the cytosol and trafficking into the nucleus.[37] The AR belongs to a class of peptides with a highly conserved amino-acid sequence. The amino terminal (hypervariable region) of the protein is characterized by a series of 22 to 28 CAG repeats encoding glutamine. Longer repeats will cause allosteric changes in the protein, interfere with the activation of transcription, and lead to variations in testosterone response.

Currently available therapies may be categorized as replacement of testosterone on the AR using testosterone or modified testosterone formulations, modulation of the AR with selective androgen receptor modifiers (SARMs), and suppression of E_2 by AIs.[37] All FDA-approved pharmacologic treatments for hypogonadism act on the AR. The choice of treatment for hypogonadism depends in part on the patient's reproductive goals and age.[37]

Testosterone Formulations

A number of testosterone formulations are available, most of which have a long history of use and well-documented efficacy and safety profiles.

Testosterone is easily absorbed from the intestine but is more than 98% metabolized by the liver in the first-pass effect. To achieve physiologic serum levels of testosterone, oral delivery requires approximately 100 times the normal daily amount of testosterone by the testes. Oral formulations have been produced by modification with a methyl group or undecanoic acid at position 17α, but both have encountered problems. Methylating prevents first-pass metabolism, but testosterone is not metabolized to DHT or , is hepatotoxic and results in a short half-life requiring multiple daily doses, and should not be used in clinical

practice.[40] Although available in Europe, Canada, and Asia, oral testosterone undecanoate (TU) has not been approved by the FDA for use in the United States. Long-acting injectable TU has been eagerly awaited in the United States but was recently rejected by the FDA pending further evaluation. (For additional information, see **Novel and Experimental Therapies for Hypogonadism**, below.) The testosterone formulations currently available in the United States are delivered as intramuscular injections, topical applications, or long-acting subcutaneous pellet implants.[40] The most commonly used formulations, accounting for 80% of the market, are topical gels.

Testosterone therapy is indicated for the treatment of men with congenital or acquired primary or hypogonadotropic hypogonadism who manifest signs and symptoms of testosterone deficiency. (See package insert for any testosterone formulation: Androgel®, Androderm®, Delatestryl®, Depo®-Testosterone, Striant®, Testim®, Testopel®.) The goal of testosterone therapy should be to restore testosterone to therapeutic levels for the primary purpose of alleviating symptoms of androgen deficiency.[41] Whether normalization of testosterone levels will prevent the morbidities associated with low testosterone levels is not yet known.

The benefits of testosterone therapy for hypogonadal men include restored libido and erectile function, heightened energy, elevated mood, improved body composition (reduced fat mass and increased lean mass and, perhaps, muscle strength), stabilized or improved BMD, and, possibly, lowered risk of fractures.[2-4] New data from the Testim Registry in the US (TRiUS) study showed that testosterone supplementation significantly improved even moderately severe to severe depressive symptoms.[11] TRiUS enrolled hypogonadal men from a variety of practice settings to receive testosterone therapy with topical testosterone 1% gel. Of the 849 men enrolled, 317 (mean age, 52 y; range, 22-84 y) returned for a 6-month follow-up visit and completed the patient health questionnaire (PHQ-9). The mean study duration was 175 days. At baseline, 83% started taking the 5-mg dose and 15%, the 10-mg dose; at 6 months, 65% were receiving the 5-mg dose and 33% were receiving the 10-mg dose. At baseline, 11% had a self-reported medical history of depression and 19.2% had moderately severe to severe depression. Baseline serum testosterone levels correlated with the PHQ-9 measures of depression: at baseline, 20.2% of men with testosterone levels <250 ng/dL had moderately severe to severe depression on the PHQ-9 versus 13.7% of men with testosterone levels >250 ng/dL. Of the 171 men with both baseline and 6-month testosterone levels, mean testosterone levels increased significantly from 242 to 463 ng/dL. PHQ-9 scores correlated with both the change in testosterone levels (P=.0005) and the mean 6-month testosterone level (P<.002). The number of patients with moderately severe to severe depression decreased from 19.2% at baseline to 7.6% after 6 months of testosterone therapy (P<.0001). In conclusion, this study found that approximately 20% of hypogonadal men (testosterone <250 ng/dL) suffer from moderately severe to severe depression, and a substantial proportion can be helped by testosterone therapy. These data underline the importance of assessing serum testosterone levels in men who present with depression.[11] Dr Seftel cautioned, however, that patients suspected of having major depression should be referred appropriately for further evaluation and treatment.

Studies have shown that achieving 400 ng/dL will restore nocturnal erections, 500 ng/dL will enable sexual intercourse, and 600 ng/dL will restore sexual desire. When treating patients in his own practice, Dr Seftel said that he usually aims for a TT of approximately 600 ng/dL.[30]

Management of Patients Receiving Testosterone Therapy

Decisions about treatment for hypogonadism and the management of hypogonadal men should be individualized with consideration for patient age, developmental status, cause and type of hypogonadism, and presence of comorbidities.[37]

In the management of hypogonadism, follow-up is as important as the initial visit and diagnosis.[30] Serum testosterone level, hemoglobin and hematocrit, and PSA testing and DRE should be performed at regular intervals. Dr Seftel posited that these will soon be mandatory for insurance reimbursement. In his talk, Dr Hellstrom recommended standard monitoring at baseline and 3, 6, and 12 months after initiation of therapy and at least yearly thereafter.[40]

Testosterone therapy is generally well-tolerated. Testicular atrophy and short-term, usually reversible aspermia with testosterone therapy are important considerations for younger patients. Clomiphene is an appropriate alternative for men who are actively trying to have children.

Sleep apnea has been reported infrequently, but its association with testosterone therapy is controversial.

Acne, oily skin, and gynecomastia have also been reported infrequently.

Fluid retention and edema occur but have little clinical relevance and are of concern only in men with class III or IV heart failure, chronic renal insufficiency, or severe liver disease.[42]

The potential for inadvertent transfer to partners or children leading to virilization with topical testosterone formulations (eg, gels or sprays) prompted a black box warning on package inserts. Injectable testosterone and testosterone patches do not have this effect. Patients using topical testosterone should be advised to air-dry for 15 minutes and wear clothing that covers the application site before coming into physical contact with women or children.

Benign prostatic hyperplasia (BPH) has infrequently worsened in men with mild or moderate lower urinary tract symptoms (LUTS); some data suggest that testosterone therapy should be avoided in men with severe LUTS.[30]

A urologist should be consulted if the PSA is above 1.4 ng/mL within any 12-month period of testosterone therapy, PSA velocity is higher than 0.4 ng/mL/y after 6 months of therapy, prostate abnormality is detected by DRE, or the AUA prostate symptom score is greater than 19. Dr Seftel routinely checks BMD for hypogonadal men, as suggested by the guidelines,[2,4,5] as well as vitamin D levels, which are often low.

Testosterone Therapy and Prostate Health

In stark contrast to conventional wisdom, numerous controlled[43-47] and noncontrolled[48-51] studies suggest that testosterone therapy does not increase the risk of developing prostate cancer. Indeed, men with low testosterone levels appear to be more likely to have biopsy-detectable prostate cancer than men with normal testosterone. In addition, results of a recent study conducted among 448 surviving participants of the Rancho Bernardo Study with no history of prostate cancer showed that a higher testosterone:DHT ratio was protective against development of BPH. The prevalence of prostate cancer in hypogonadal men with PSA levels of 4.0 ng/dL or lower does increase as the PSA increases. In a moderated podium session, J. Kellogg Parsons presented results of an 8.4-year follow-up study to evaluate the risk of clinical BPH in a cohort of 448 surviving participants of the Rancho Bernardo Study. Patients had no history of prostate cancer. Independent of age, the highest quartile of testosterone:DHT correlated with a 47% decreased risk of BPH compared with the lowest quartile, whereas higher serum DHT increased the risk of BPH.[52] Dr Seftel, therefore, recommended performing a biopsy before starting treatment if the PSA level is 3.0 ng/dL or greater.

A 2004 report of testosterone therapy after curative radical prostatectomy for 7 men with localized prostate cancer from two urologic practices showed no biochemical or clinical evidence of cancer recurrence after follow-up periods.[53] The authors concluded, "Based on the clinical experience with this small group of men, and indirect evidence of the safety of this approach from epidemiologic and clinical data, further cautious use of testosterone in a carefully selected population seems warranted."

Two studies presented at AUA 2010 also explored this topic with similar results. According to the Endocrine Society guidelines and recommendations of the International Society of Andrology (ISA), International Society for the Study of the Aging Male (ISSAM), European Association of Urology (EAU), European Academy of Andrology (EAA), and American Society of Andrology (ASA), symptomatic hypogonadal men who have undergone successful treatment for prostate cancer and have no evidence of residual disease are potential candidates for testosterone therapy "after a prudent interval."[5] In his presentation for allied health professionals, Dr Seftel suggested that testosterone should not be prescribed for this population until large, well-designed clinical trials have established its safety and efficacy. The use of testosterone therapy for hypogonadal men after radical prostatectomy for prostate cancer is a controversial topic, and most of the studies to date have been small. Two original research presentations at moderated Podium Session 43 explored this topic:

- To add to the database, a European retrospective study of 69 men (median age, 56 y; range, 43-66 y) who received testosterone therapy for ≥6 months after curative radical prostatectomy for organ-confined prostate cancer. All subjects had Gleason grade ≤6, negative surgical margins, no adjuvant therapy, and PSA <0.1 ng/mL (undetectable) at initiation of testosterone therapy. Median time from surgery to initiation of testosterone therapy was 24 months. To ensure rapid discontinuation if necessary, patients used testosterone gel for the first year and then switched to long-acting injectable testosterone. Serum testosterone increased significantly (P<.001). No patient had evidence of biochemical recurrence after a median follow-up of 19 months (range, 6-72 mo). In the absence of large, randomized, controlled trials, these results add to the available evidence that testosterone can be safely offered to selected post-radical prostatectomy patients with hypogonadism.[54]

- In this retrospective study, 133 post-radical prostatectomy hypogonadal men (mean age, 65 y) received testosterone therapy (Testim®) a mean of 151 days after surgery and were followed for a mean of 363 days. Of these, 21 were classified as high risk (8 with Gleason ≥8, 16 with positive margins,1 with node-positive disease). No biochemical recurrences or statistically significant increase in PSA occurred: Mean PSA at baseline and at 3, 6, 9, 12, and 15 months of treatment was 0.003, 0.016, 0.011, 0.010, 0.010, and 0.01 ng/mL, respectively. This study is the largest series in the literature on the use of testosterone therapy after radical prostatectomy and the first on the use of testosterone therapy in high-risk post-radical prostatectomy patients. Although these results are encouraging, large, randomized, controlled trials are needed.[55]

Testosterone may be given, with caution and close follow-up, to selected patients after brachytherapy.[30] Among 31 men given testosterone starting 0.5 to 8.5 years after brachytherapy and followed for periods ranging from 1.5 to 9 years, PSA remained under 1.0 ng/dL in all and under 0.1 ng/dL in nearly three-quarters of the patients, with no evidence of cancer recurrence or documented progression.[56]

Testosterone Therapy and Cardiovascular Risk

It was long assumed that the higher incidence of CV events among men compared to women resulted from higher testosterone levels and that,

therefore, testosterone therapy would increase CV risk.[25] In fact, as discussed above, low rather than high endogenous testosterone levels appear to predispose men to heart disease; studies of testosterone therapy have not demonstrated an increased risk of CVD or CV events, such as MI, stroke, or angina, and suggest some benefit to restoring normal physiologic testosterone levels.[57] The effect on lipids is generally neutral or slightly beneficial.[25,57] English et al, for example, found greater angina-free exercise tolerance among 22 men with chronic stable angina treated with transdermal testosterone therapy compared with 24 control subjects.[58] A recent metaanalysis of 30 trials involving 1642 men demonstrated that testosterone therapy is not associated with important CV effects.[25,59] These results are reassuring, but large randomized, placebo-controlled, prospective trials are needed to assess the long-term consequences of testosterone therapy. There is still a paucity of data on the risk of very high testosterone levels and no data on the rate of increase of testosterone levels.[25]

Novel and Experimental Therapies for Hypogonadism

Testopel®

Considerable interest in this newly available, long-acting formulation of testosterone was apparent at AUA 2010. Testosterone pellets received approval by the FDA in the 1970s, however, pharmacokinetic data are limited. It is currently the only long-acting testosterone formulation approved for use in the United States.

During Course 112HO, *Hands-on Office Treatment of Male Sexual Dysfunction*, Mohit Khera, MD, provided information on the background, efficacy, and safety of Testopel® and detailed instructions—including a video—for how to insert them. After the lecture section of the course, participants attended a workshop in which they were able to handle and practice with a variety of methods for treating male sexual dysfunction, including pellet insertion. Dr Khera cautioned that it is necessary to go deep into the subcutaneous fat to avoid nerves. The technique is relatively easy to master and can be done in an office setting in about 10 minutes. Training videos are available from the manufacturer. When implanteed properly, extrusion of the pellets is rare, and techniques such as “V” insertion and stacking of the pellets can further reduce the risk of extrusion.

The pellets are cylindrical, 3.2 mm (~1/8”) in diameter and 8 to 9 mm in length. Each sterile pellet weighs about 77 mg (75 mg of which is testosterone) and is supplied ready for subcutaneous implantation.[30] Pellets dissolve slowly in the adipose tissue and can raise a patient’s testosterone levels for 3 to 6 months.

Patients should be advised not to swim, use a hot tub, or lift heavy weight for a few days after the pellets are placed but may otherwise resume normal activities immediately after insertion. The pressure dressing can be removed after 24 hours and the Steri-Strip after 48 hours. Potential complications include bleeding, infection, extrusion, persistent pain, and marginal or no improvement in serum testosterone levels. Dr Khera said that he initially prescribed Vicodan for injection-site pain but now considers that “overkill”; over-the-counter ibuprofen is sufficient,

but even that is often not needed. Antibiotics are not given routinely as infection is rare.

Some presurgery considerations include whether the patient is taking anticoagulants or has a history of prostate cancer, rising PSA, CVD, or renal or hepatic insufficiency. As with all testosterone preparations, edema is a potential risk. Because the pellets are long-lasting and therapy cannot be quickly stopped, Dr Khera advised starting with a low dose. The use of testosterone pellets in patients with a history of prostate cancer is controversial, primarily because of the inability to stop therapy quickly in the event of rising PSA. Unlike with some other preparations, erythrocytosis is unlikely because of the lack of a testosterone surge. Reimbursement issues should also be considered. Insurance coverage has improved greatly but is not universal, so healthcare providers must be aware of the situation for their patients.

Absorption is very rapid, so blood must be drawn before implantation. Dosage (number of pellets) must be individualized. The appropriate dose for most men will be 10 to 12 pellets. Blood levels must be monitored at 1 and 3 months and the next dose must be adjusted accordingly. Once the appropriate dosage is determined, testosterone levels remain consistent. Although occasionally implants may be effective up to 6 months, reimplantation will usually be necessary after 4 to 5 months.

Four adverse events (AEs) were reported in the pivotal trial of Testopel®: self-limiting contact dermatitis to the Steri-Strips occurring 2 days after the procedure; self-limiting local insertion-site reaction (eg, pruritis, erythema, edema) occurring 2 months after the procedure; one local infection of the insertion tract 7 days after the procedure in a patient who failed to follow post-surgery instructions (he used a hot tub after the procedure); and one immunologic reaction requiring pellet removal. One-third of the patients had previously used another testosterone formulation; of these, two-thirds indicated a preference for the pellets.[60]

Long-Acting Testosterone Undecanoate for Injection

Long-acting injectable TU has been in use in more than 100 countries as Nebido® since 2003, and the pharmacokinetic, efficacy, and safety profile of the 1000-mg dose has been well-documented in numerous publications.[40] More recent studies have shown the safety and efficacy of the 750-mg dose being evaluated in the United States. Testosterone levels are in the physiologic range for the 10-week dosing interval and remain in the normal range during consecutive injection intervals.[61-63] The mean total mood disturbance score improved significantly (Figure 2), improvements were noted on all subscales,[64] and improvements in erectile function symptom scores are similar to those demonstrated with the 1000-mg dose.[40,64,65]

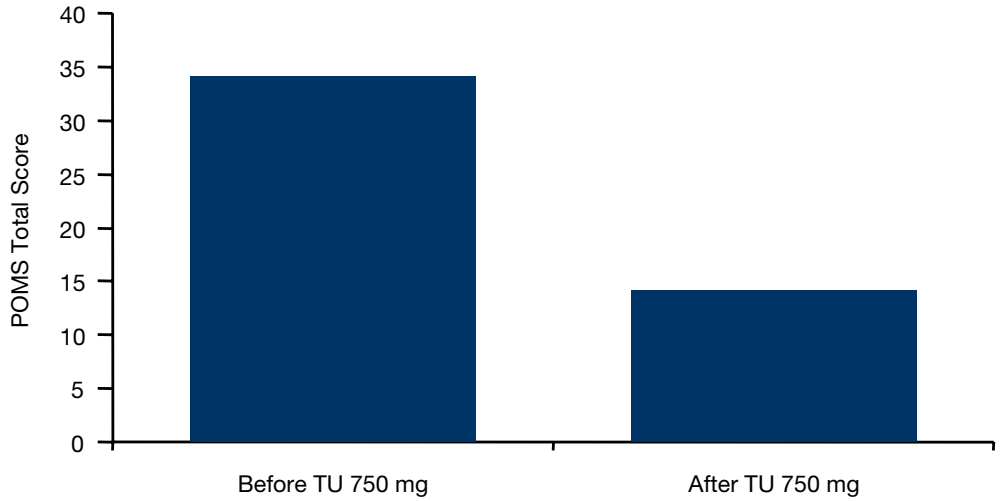
This formulation has been generally well-tolerated. Treatment-related AEs tend to be mild and nonserious.[61-63] The most common AEs occurring in ≥5% of patients are acne and injection-site pain.

TU for injection is currently being reviewed by the FDA as Aveed®. Expected to be approved late in 2009, the FDA requested additional information and strengthening of the manufacturer's risk evaluation and mitigation strategy for the drug. It has been reported to rarely cause acute pulmonary symptoms immediately after injection. It is postulated that these symptoms may be due to an anaphylactic reaction or a pulmonary oil microembolism.

Selective Androgen Receptor Modulators

SARMS are nonsteroidal modulators of the AR and are both more selective and more potent than testosterone formulations.[37]

Figure 2. Profile of Mood States overall in 120 hypogonadal men treated with testosterone undecanoate 750 mg every 12 weeks for 48 weeks.[40,63]



P<.05.
Hypogonadism was defined as morning TT <300 ng/dL; the mean baseline TT was 186 ng/dL.
POMS, Profile of Mood States; TT, total testosterone; TU, testosterone undecanoate.

Of the various classes of molecules that might function as SARMs, the most extensively studied are aryl propionamides, bicyclic hydantoins, quinolinones, and tetrahydroquinolones.[37] Most of the current research has focused on development of nonsteroidal AR agonists designed with predominantly anabolic activity to address bone structure and muscle weakness, but there has also been interest in developing tissue-selective AR antagonists and steroidal SARMs to manage sexual dysfunction.[37]

A number of SARMS are in various stages of development,[37,66] and a limited number have reached clinical trials. In this exciting area, research will discover new pathways for intervention, and specialized SARMs will increase efficacy and tissue specificity while decreasing AEs.[37]

Selective Estrogen Receptor Modulators

Depending on their structure, SERMs may have purely antagonistic or mixed agonist/antagonist activity.[37] No SERM has been approved by the FDA for treatment of hypogonadism; however, clomiphene (Clomid®) has been used for more than 20 years for men who have low FSH and LH. Many experts consider treatment with clomiphene to be an option for

younger hypogonadal men concerned with maintaining fertility, because it will increase FSH and LH levels, stimulate spermatogenesis, and increase testosterone levels, but hypogonadism treatment is an off-label use. Clomiphene may significantly increase E_2 levels due to increased LH; therefore, patients should be monitored carefully. A study presented at AUA 2010 reported sustained elevations of testosterone levels with long-term treatment, but after an initial decline, Androgen Deficiency in Aging Males (ADAM) scores increased significantly and E_2 levels increased steadily and significantly during treatment. This study found clomiphene to be most effective among men younger than 55 years of age.[67] As mentioned, clomiphene for the treatment of hypogonadism has been used primarily for younger men concerned about fertility. This study evaluated clomiphene for older men. The study population included 96 hypogonadal men (mean TT at baseline, 242 [±47] ng/dL), with a mean age of 61 years (range, 50-70 y); slightly more than one-third had hypertension and dyslipidemia, and 14% had diabetes. Testosterone levels increased into the normal range for 76% of men, and ADAM scores significantly decreased from 7 (±1.5) to 4 (±3) (P>.01). At baseline, 77% of subjects had abnormal bone density and 22% had osteoporosis. After 12 months of treatment, bone density remained abnormal in 83% of those with osteopenia and 38% of those with osteoporosis. Patients who were younger (age, <55 y) and healthier (≤2 comorbidities), did not have diabetes, and had lower LH levels (<2.0) were most likely to achieve a testosterone level ≥400 ng/dL.[67]

To date, no published trials have addressed the long-term effects of clomiphene in men. Katz et al evaluated the efficacy and safety of clomiphene in 46 hypogonadal men treated for ≥12 months (37 for ≥24 months; 29 for ≥ 36 months).[68] The starting dose was clomiphene 25 mg every other day. Three-quarters of the group continued taking this dose for the duration of treatment; for the remainder, the dose was titrated to a maximum of 50 mg every other day, then 50 mg daily as needed, before testosterone supplementation. Statistically significant increases in TT levels and bone density scores were sustained over the course of treatment, but ADAM scores increased again after an initial decrease (baseline, 7 [±2]; 12 months, 3 [±2]; 36 months, 5 [±3]). E_2 levels increased steadily and significantly over the course of treatment from a mean of 37 (±16) at baseline to 50 (±30) at 36 months (P=.02).[68]

Enclomiphene (Androxal®) is an isomer of clomiphene that significantly increases testosterone levels, but long-term effectiveness and safety have not been evaluated, and Androxal® is not approved for use in the United States.

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