

# American Urological Association

---

## Conference Courier Highlights Report on Hypogonadism

**TU TestosteroneUpdate**<sup>®</sup>  
Collaborative for Improved Clinical Outcomes in Hypogonadism  
[www.TestosteroneUpdate.org](http://www.TestosteroneUpdate.org)

Collaborative for Advancement of  
Urologic ■ Sexual ■ Endocrine education  
[www.CAUSEducation.org](http://www.CAUSEducation.org)

CAUSE is a multi-funded initiative generously supported by

 **ENDO** and  **Lilly**

  
**CAUSE**  
education

  
**CONFERENCECOURIER**<sup>®</sup>  
*Bringing Medical Conferences to You*

Jointly sponsored by the **Annenberg Center for Health Sciences at Eisenhower** and **CogniMed Inc.** This activity is supported by  
an independent educational grant provided by **Endo Pharmaceuticals.**

## **American Urological Association**

---

### Conference Courier Highlights Report on Hypogonadism

Hypogonadism and its treatment was one of the state-of-the-art topics at the annual meeting of the American Urological Association April 24 to April 30, 2009, in Chicago, Illinois. Hypogonadism is a clinical condition characterized by abnormally low levels of testosterone in the presence of one or more signs or symptoms (Table 1).<sup>1-4</sup> The purpose of this Conference Courier is to briefly review the information and newest data on hypogonadism and its treatment presented at AUA 2009.

# Table 1. Signs and Symptoms Suggesting Hypogonadism<sup>1-3</sup>

Signs	Symptoms	
	Sexual	Nonsexual
<p>Low endogenous testosterone</p> <p>Testicular atrophy</p> <p>Anemia</p> <p>Reduced bone mineral density (osteopenia or osteoporosis)</p> <p>Changes in body composition (↑ fat mass, ↓ lean body mass)</p> <p>Oligospermia, azoospermia</p>	<p>Loss of libido</p> <p>Erectile dysfunction</p> <p>Difficulty achieving orgasm</p> <p>Reduced intensity of orgasm</p> <p>Diminished ejaculatory volume</p> <p>Decreased sexual sensation in the genital region, particularly the penis</p>	<p>Reduced sense of vitality or “energy” (lethargy)</p> <p>Increased fatigue</p> <p>Depressed mood</p> <p>Reduced motivation</p> <p>Decreased muscle mass or strength</p> <p>Impaired cognition</p>

# Hypogonadism and Testosterone Therapy in Current Urologic Practice

Approximately 200 people attended this course presented by Wayne JG Hellstrom, MD (Course Director), and Craig F Donatucci, MD. Dr Hellstrom introduced the course by briefly reviewing the pathology and multifactorial etiology of hypogonadism (aging, disease, habits, medication); normal testosterone metabolism; age-related decline in testosterone and its complications; and the incidence and prevalence of hypogonadism, which occurs at higher rates in men who have diabetes, AIDS, chronic renal failure, rheumatoid arthritis, or chronic liver disease or who use glucocorticoids or neuroleptic agents.<sup>3,5</sup>

Hypogonadism is suggested by the presence of signs and clinical symptoms and confirmed by a laboratory finding of low serum testosterone levels. Because of its diurnal variation, serum total testosterone (TT) ideally should be measured in the morning.<sup>2,4</sup> Reduced libido is the hallmark of hypogonadism, but not by any means the only symptom (Table 1).<sup>1-4</sup> The nonsexual symptoms of hypogonadism are nonspecific, thus requiring a high degree of suspicion on the part of the examining physician.

- No consensus exists on the threshold level of testosterone that is diagnostic of hypogonadism, but a TT level of 300 ng/dL is generally considered the lower limit of normal.<sup>1,6,7</sup> Physicians should be aware that laboratory reference values for testosterone vary widely between different laboratories. That being said, as a general rule, men with TT <200 ng/dL clearly are hypogonadal; men with TT >400 ng/dL are unlikely to be hypogonadal; and men with TT between 200 and 400 ng/dL should be evaluated on the basis of clinical presentation. Any patient who is symptomatic, whether testosterone levels are abnormally low or in the low-normal range, should be considered for therapy with exogenous testosterone. Physical examination appropriately includes stature, body hair (amount and distribution), presence of gynecomastia or galactorrhea, flaccid penis length and width (stretched), scrotum, testes (length, width, consistency), and prostate.<sup>2</sup> Screening questionnaires, such as the Androgen Deficiency in Aging Males (ADAM) questionnaire,<sup>8</sup> the Aging Male Survey (AMS),<sup>9</sup> and the Massachusetts Male Aging Survey (MMAS),<sup>10</sup> have been developed to assist in the diagnosis of hypogonadism. Raymond C Rosen, PhD, and colleagues at the New England Research Institutes are developing a hypogonadism screening tool with improved specificity that may be useful for patient-reported outcomes in future clinical studies.<sup>11</sup>

Dr Hellstrom then addressed the treatment of hypogonadism. The potential benefits of testosterone therapy include improved mood, libido, body composition, and bone mineral density (BMD). However, determining an appropriate dose of exogenous testosterone is challenging because the levels of testosterone required for various androgen-dependent functions appear to differ and the amounts needed to maintain those functions are not known. The low doses of exogenous testosterone that normalize libido, for example, may be insufficient for other androgen-dependent processes.

The ideal testosterone therapy should be safe, effective, convenient, inexpensive, and acceptable to patients; have predictable pharmacokinetics and a low potential for abuse; and should help attain normal physiologic dihydrotestosterone (DHT) and estradiol (E<sub>2</sub>) levels and physiologic or near-physiologic levels with a natural diurnal pattern (morning peaks, evening nadirs). A number of testosterone products are available:

- Transdermal patches are available for application to nonscrotal skin, are effective, and mimic normal circadian variations. Transdermal patches require a permeation-enhancing vehicle, and application site reactions are common. Spray-on androgen delivery systems are in development.
- Testosterone gel preparations provide easy, effective, and invisible treatment options and account for >80% of the US market. Skin irritation is not usually a problem. Application to multiple sites is recommended, but a small study (N=9) found no difference in efficacy between multiple-site and single-site application.<sup>12</sup> Men using gels must wait 5 to 6 hours after application to shower or swim. A boxed warning was added to testosterone gel formulation labels after the US Food and Drug Administration received reports of adverse effects in children who were inadvertently exposed to testosterone through contact with another person being treated with these products (secondary exposure). Reports included inappropriate genitalia (penis or clitoris) enlargement, premature pubic hair development, advanced bone age, increased libido, and aggressive behavior.<sup>13</sup>
- Testosterone pellets for subcutaneous implantation have been approved in the United States since 1972, but many clinicians are not aware of this formulation. The prescribing information specifies implanting two 75-mg pellets weekly for each 25 mg testosterone propionate required. A typical dose is six to ten 75-mg pellets (~3 mm x 8 mm) implanted in the posterior gluteal region every 3 to 6 months. Dosage titration is required. In addition, great care should be taken when estimating the amount of testosterone needed, because pellet implantation is much less flexible than oral medication or intramuscular injection. Approximately one third of testosterone pellet material is absorbed in the first month, one fourth in the second month, and one sixth in the third month.<sup>14</sup> Treatment effect may last from 3 to 6 months.<sup>14</sup> The most bothersome adverse events were pellet extrusion, bleeding, and infections.<sup>15,16</sup> New data for testosterone pellets are reviewed later in this article.

- Intramuscular injection of testosterone enanthate or testosterone cypionate (100-300 mg) achieves testosterone levels in the supraphysiologic range within 72 hours, and levels decrease into the hypogonadal range by the end of the dosing interval.<sup>1,2</sup> Administered once every 1, 2, or 3 weeks or once a month, these formulations are associated with wide variations in serum testosterone levels that can lead to a roller-coaster effect, characterized by undesirable swings in mood, energy, libido, and sexual function, which some patients find disagreeable.<sup>1,2,17</sup>
- Long-acting testosterone undecanoate (TU) in castor oil for intramuscular (IM) injection is under review by the FDA.<sup>18</sup>
- This formulation has been approved in more than 80 countries worldwide. The product is generally well tolerated. Efficacy is consistent with the known beneficial effects of testosterone therapy: clinically therapeutic levels of TT and FT, DHT, E<sub>2</sub>, sex hormone-binding globulin (SHBG); no clinically significant changes in prostate-specific antigen (PSA) levels or findings on digital rectal examination (DRE)<sup>19-22</sup>; and significant improvements in sexual function.<sup>23</sup> Updated pharmacokinetic data on TU are reviewed later in this article.

Concerns about exogenous testosterone therapy and apparent associations with prostate cancer and cardiovascular disease (CVD) are ongoing. Recent evidence suggests the opposite: androgen-deprivation therapy (ADT) increases the risk of peripheral arterial disease (PAD), cardiac events, and cardiac death, and higher (but physiologically normal) levels of testosterone may be protective.<sup>24-27</sup> Furthermore, testosterone deficiency is associated with an increased all-cause mortality<sup>28,29</sup>; and lower levels of endogenous testosterone may increase the risk of prostate cancer and have been linked to worse prognosis, higher stage at presentation, and higher grade cancers.<sup>30</sup> No compelling evidence exists that testosterone therapy increases the risk of developing prostate cancer or of stimulating the progression of small, undetected tumors into clinically worrisome disease.<sup>31-33</sup>

Adverse events with testosterone include erythrocytosis, particularly in men who are older, live at high altitudes, or receive short-acting parenteral testosterone therapy,<sup>34,35</sup> and acne. Gynecomastia is uncommon. Although the mechanism is not understood, testosterone therapy has been associated with new onset or exacerbation of sleep apnea.<sup>36</sup> Most men receiving exogenous testosterone will be azoospermic or have severely depressed sperm concentration, which may result in reduced testicular size. Although these effects are usually reversible after cessation of testosterone therapy, clomiphene citrate and gonadotropins may be better choices for hypogonadal men wishing to have children in the near future. Results of a recent study of clomiphene citrate are reviewed later in this article.

Men receiving exogenous testosterone should be assessed for changes in the clinical symptoms and signs of testosterone deficiency by DRE, serum testosterone and PSA levels, and hematocrit at baseline, at 3 to 6 months after initiating therapy, and annually thereafter. Monitoring with liver function tests is usually unnecessary, because liver toxicity is a problem only with oral forms of exogenous testosterone.<sup>1,17</sup>

# Should Hypogonadal Men With a History of Prostate Cancer Be Treated With Testosterone?

The importance of, and interest in, this topic is attested to by the key sessions during which it was discussed. The field has changed rapidly. In 1988, testosterone therapy during men with a history of prostate cancer was unthinkable; today, a greater number of physicians are treating patients who have been successfully treated for prostate cancer, but it remains controversial. Both the Sexual Medicine Society of North America (SMSNA) Annual Scientific Program and the Plenary Session addressed the issue in debate formats. In the SMSNA Program, Irwin Goldstein, MD, and Abraham Morgentaler, MD, acted as moderators; Craig F. Donatucci, MD, President of the SMSNA, introduced the Program; and pro and con arguments were presented by Ridwan Shabsigh, MD, and Gerald B. Brock, MD, respectively. The Plenary Session: Point-Counterpoint was moderated by Randall B. Meacham, MD, with pro and con arguments by Abraham Morgentaler, MD, and Alvaro Morales, MD, respectively.

## **Arguments in Favor of Testosterone Therapy for Hypogonadal Men With Prostate Cancer**

The importance of androgens in progression of prostate cancer was first noted by Huggins and Hodges in 1941.<sup>37</sup> Careful reading of that study, however, reveals that the paradigm that has guided management of prostate cancer for 68 years was based on a single patient.<sup>32,37</sup> Furthermore, the data from several key studies<sup>32,38,39</sup> have been misinterpreted. These studies made an important distinction between men who have been previously castrated, for whom testosterone therapy is absolutely contraindicated, and men who have not been castrated, in whom progression of prostate cancer

was not seen. Analyses of prospective studies in the literature have found no evidence that exogenous testosterone increases the risk of prostate cancer or causes regression of prostate cancer in men who have not been castrated.<sup>33,40</sup>

In his argument, Dr Morgentaler cited the case of one of his own patients, an 84-year-old man with Gleason 6 prostate cancer in both lobes and PSA of 8.1 to 8.5 ng/mL, with symptoms of hypogonadism, low-normal TT, and abnormally low FT, who refused treatment for prostate cancer but requested testosterone therapy.<sup>41</sup> After 2 years of treatment, the patient had no evidence of clinical progression of prostate cancer and had a lower PSA level.

Much of the rationale in favor of testosterone therapy for men who have localized prostate cancer comes from data on prostate cancer itself:

- Testosterone has never been shown to cause prostate cancer
- Most men with prostate cancer die of CVD, not of prostate cancer
- Castration is not an appropriate therapy for localized prostate cancer
- Cure is common with localized prostate cancer
- Watchful waiting is advocated for localized prostate cancer, emphasizing the importance of quality of life (which includes sexual function)

Arguments for treatment also come from the science of testosterone therapy. Hypogonadism has numerous quality-of-life, cardiovascular, and other systemic consequences, including premature mortality.<sup>29,42</sup> ADT is associated with increased risk of diabetes and CVD.<sup>43</sup> Studies have shown that testosterone does not change prostate tissue; and men have been treated safely after prostatectomy<sup>44,45</sup> and brachytherapy.<sup>46</sup>

The argument for treatment is supported by the molecular biology of androgen receptors (ARs). The limited number of ARs per cell are completely bound to androgen at androgen levels in the near-castrate range. Dr Morgentaler's proposed saturation model accounts for both the seemingly contradictory data and the molecular biology of androgen-AR interactions (Figure 1).<sup>47</sup>

Dr Shabsigh concluded that testosterone therapy for men with localized or successfully treated localized prostate cancer is "reasonable, rational, logical, and indicated."

#### **The Endocrine Forum: Prostate Cancer and Testosterone**

In front of an audience of 500 with standing room only, during the Endocrine Forum: Prostate Cancer and Testosterone—Changing Concepts, Drs Mohit Khera, Abraham Morgentaler, Larry I. Lipshultz, Peter Albertsen, and Ernani Rhoden discussed the treatment of patients after definitive prostate cancer treatment. Thus far, 147 patients have been treated after prostate cancer treatment, and only 1.4% were noted to have recurrence. Dr Khera reviewed the parameters for a randomized, controlled clinical trial to investigate testosterone therapy in hypogonadal men 3 months after prostatectomy.

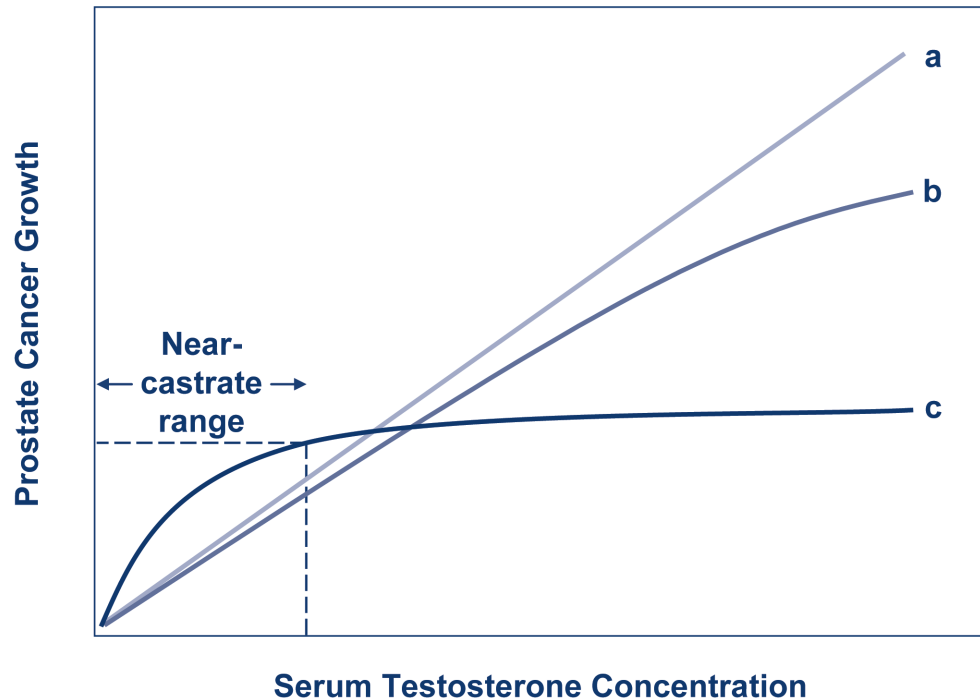
#### **Data From a Recent Case-Cohort Study**

Further evidence for a lack of association between testosterone and the risk of prostate cancer was presented by Nicholas A Daniels, MD, in a podium presentation. In a case-cohort study within the ongoing Osteoporotic Fractures in Men (MrOS) study,<sup>48</sup> investigators evaluated the risk of prostate cancer associated with circulating sex hormones in men  $\geq 65$  years of age (275 patients with prostate cancer, 1652 control volunteers; mean age, 73 y). Gas chromatography/tandem mass spectroscopy—the gold standard—was used to measure hormone levels. Men with a history of prostate cancer or androgen/anti-androgen therapy were excluded. The groups were categorized into quartiles by sex hormone levels. No significant association was found between the risk of prostate cancer and circulating testosterone, E<sub>2</sub>, or SHBG, but increasing levels of estrone were strongly correlated with an increased risk of prostate cancer: hazard ratio (HR) 3.93 for quartiles 2 to 4. Limitations of this study include a follow-up of only 5 years and a single measurement of baseline hormone levels. Dr Daniels posited that, although further study is needed, these results suggest the possibility of estrone as a biomarker for the risk of prostate cancer.

#### **Arguments Against Testosterone Therapy for Hypogonadal Men With Prostate Cancer**

There is no question about the importance of testosterone therapy for hypogonadal men without prostate cancer. Furthermore, many experts agree that testosterone therapy can and often should be given to men who have been successfully treated for prostate cancer. However, there are serious questions about its safety in men who have prostate cancer.

Figure 1. Relationship between testosterone and prostate cancer: the saturation model.<sup>47</sup>



a and b, traditional belief that higher concentrations cause increasing prostate cancer rates; c, saturation model, testosterone has powerful effect on prostate cancer growth at low testosterone concentrations but little or no effect beyond the near-castrate range.

Reproduced with permission.

That testosterone plays a key role in development and progression of prostate cancer has been dogma since the 1940s, and experiments with luteinizing hormone-releasing hormone (LHRH) agonists further linked testosterone to prostate cancer. To assess whether testosterone is safe in men with a history of prostate cancer, one must look critically at clinical trials. Are they randomized, controlled, well designed, and adequately designed? What detection method was used? PSA as a surrogate marker for prostate cancer is often not an appropriate endpoint. Importantly, what was the duration of testosterone therapy? Prostate cancer takes many years, not weeks or months, to develop and progress to clinically important stages, but a number of studies cited by those supporting testosterone therapy for men with prostate cancer had insufficient or short-term follow-up. Many of the 18 studies were not designed to detect such changes. The study by Marks et al<sup>31</sup> on prostate tissue, for example, was a short-term study with only 21 patients receiving testosterone therapy (plus 19 receiving placebo), and analysis excluded the outliers.

A major concern in this field is the treatment of men after prostatectomy, and further studies are warranted. The most powerful argument against treating is the Physicians' Health Study,<sup>49</sup> which concluded that long-term exposure to high levels of endogenous bioavailable testosterone—and perhaps to low levels of E<sub>2</sub>—promotes the development of prostate cancer.

Dr Brock, concluding for the con position, stated that, whereas current studies are insufficient in terms of duration, design, and chosen endpoints, testosterone therapy may be safe in symptomatic men after curative prostate cancer surgery. However, large-scale longitudinal studies are needed.

In conclusion, the association of testosterone therapy with prostate cancer is not clear and is likely not a 1:1 relationship. Long-term data are still needed. Men with prostate cancer should be given testosterone only in well-designed clinical trials and with close monitoring.

#### **Post-SMSNA Program Discussion**

During the moderated discussion of case studies and audience questions after the SMSNA Program, most attendees indicated that they would treat a symptomatic hypogonadal patient after radical retropubic prostatectomy (RRP) if the nodes and margins were negative. The most pressing question is when to initiate therapy. Studies are under way, but data are not yet available. The SMSNA Program panel agreed that, after recuperating from the surgery (usually 6-8 wk), if the patient is hypogonadal, symptomatic, and requests therapy, treatment may be considered with careful monitoring. When deciding whether to treat, the patient's wishes and quality of life should be given priority. Whether to treat depends on the individual, and informed consent is crucial.

# Endothelial Dysfunction: A Link Between CVD and Hypogonadism?

Hypogonadism, which is common in older men, is associated with endothelial dysfunction and carotid intima-media thickness,<sup>50-52</sup> both of which are factors in the development of CVD. ADT is known to be associated with an increase in cardiovascular events,<sup>53</sup> and mounting evidence suggests a relationship between low testosterone levels and CVD,<sup>28</sup> but no study to date has directly linked CVD and hypogonadism.

## **Possible Association Between CVD and Hypogonadism**

As part of the ongoing World Trade Center Medical Monitoring and Treatment Program, Berookhim and colleagues<sup>54</sup> evaluated the relationship between hypogonadism (testosterone <300 ng/dL) and coronary artery calcium (CAC) score. CAC scores above the 75th percentile indicate a risk of future cardiovascular events, and doubling of the CAC score increases the risk by 20%.<sup>55</sup> Of the 150 men studied, 15% were in the highest CAC risk group. Results showed a strong trend (Table 2) suggesting a relationship between CAC scores and CVD,<sup>54</sup> which the investigators believe will become statistically significant with more patients and longer follow-up. A limitation of this study was a lack of oversight to ensure that testosterone was based on morning draws. In addition, the validity of CAC scores to predict cardiovascular events is hotly debated among cardiologists.<sup>56</sup>

## **Association Between Endothelial Dysfunction and Low Serum Testosterone Levels**

Mohammed et al<sup>57</sup> evaluated the association between endothelial dysfunction and low endogenous testosterone levels. In this study, presented by John S. Colen, MD, endothelial function in 56 men presenting with erectile dysfunction (ED) was determined by peripheral arterial tonometry (PAT), which measures the magnitude of arterial tone changes in peripheral arterial beds. The men were divided into hypogonadal and eugonadal groups (testosterone  $\leq$ 350 ng/dL vs >350 ng/dL), then further stratified into those with or without endothelial dysfunction (RHI  $\leq$ 2.0 vs RHI >2.0). Low testosterone levels correlated with endothelial dysfunction ( $r=0.35$ ,  $r^2=0.12$  Nagelkerke;  $P=.032$ ). Interpretation of these results is limited by the small patient numbers; employing a relatively high testosterone level, for statistical purposes, to define hypogonadism; and using an indirect measure of endothelial dysfunction. Additional studies, including clinical trials in a larger population, are under way to better define the association described here.

Table 2. Association of Coronary Artery Calcium Scores With Testosterone Levels in Hypogonadal Men<sup>54</sup>

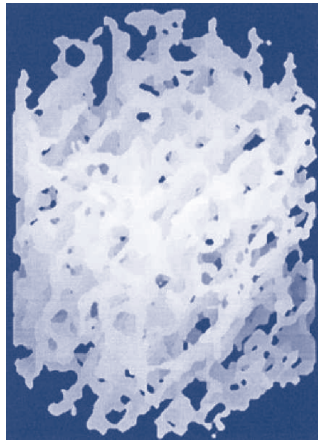
Percentile (n)	Median Testosterone Level, ng/dL	Men With Hypogonadism (n)
0-74 (109)	362	23.9 (26)
75-89 (49)	376	22.4 (11)
90-99 (28)	322	42.9 (12)

Reproduced with permission.

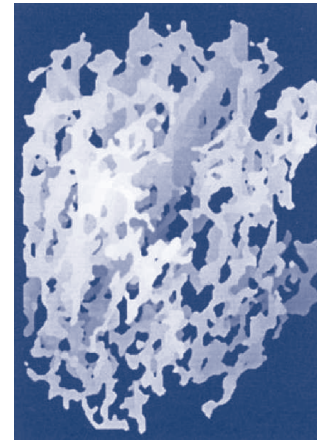
# Intramuscular Testosterone Undecanoate Improved BMD in Hypogonadal Men With Klinefelter Syndrome

Klinefelter syndrome is related to testicular insufficiency leading to low circulating levels of testosterone and lower-than-normal bone mineral density (BMD).<sup>2</sup> In men without Klinefelter syndrome, abnormally low levels of endogenous testosterone have been associated with poor bone quality or osteoporosis (Figure 2)<sup>58</sup> and with an increased risk of bone fractures (Figure 3).<sup>59</sup> Testosterone therapy is recommended to improve BMD.<sup>1,2,4</sup> At a Moderated Poster session, Tae Hong Kim, MD, presented a Korean study<sup>60</sup> on the effect of IM testosterone undecanoate (1000 mg/4 mL) on BMD in 12 men with Klinefelter syndrome. From January to December 2006, patients received 6 doses of testosterone undecanoate at 12-week intervals, which resulted in significant increases in testosterone and BMD in the lumbar spine and femoral neck (Table 3). Dr Kim concluded that testosterone therapy may help to prevent fractures of the lumbar spine and femoral neck in patients with Klinefelter syndrome.

Figure 2. Loss of sex hormones in hypogonadal men adversely affects bone quality, as shown in these 3-dimensional projection images of virtual bone biopsy cores of two men: a 28-year-old, white eugonadal man (left) and a 31-year-old, white hypogonadal man (right).<sup>58</sup>



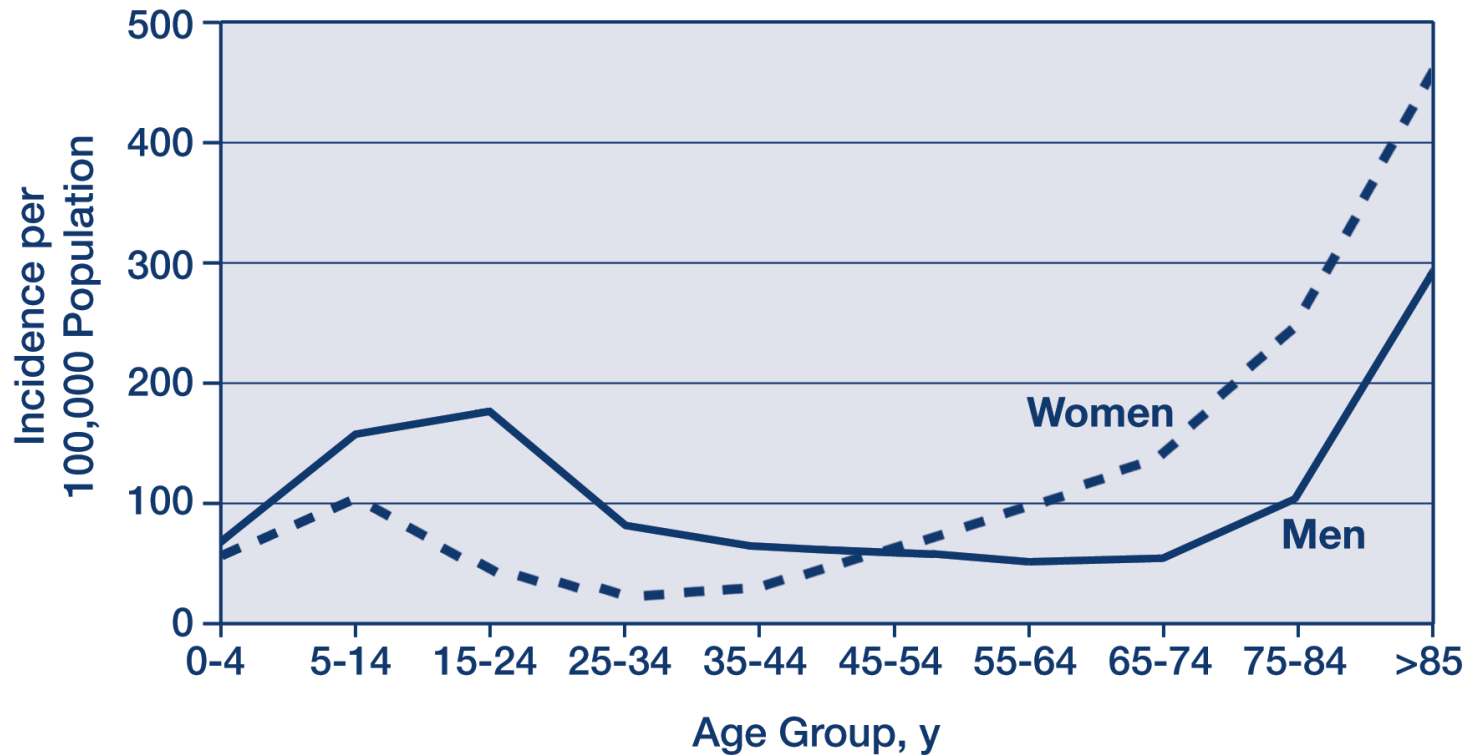
Well connected, predominantly platelike trabecular network of the age-matched volunteer's bone quality



More disconnected, predominantly rodlike architecture of the hypogonadal man's bone quality

Reproduced with permission.

Figure 3. Increased incidence of fracture: a long-term consequence of andropause.<sup>59</sup>



Reproduced with permission.

### Table 3. Effect of Intramuscular Testosterone Undecanoate on 12 Korean Men With Klinefelter Syndrome<sup>60</sup>

	Baseline (SD)	After Treatment (SD)	<i>P</i>
Total testosterone, ng/dL	195 (150)	535 (233)	.001
BMD			
Lumbar	0.88 (0.06)	0.95 (0.06)	.04
Ward's triangle	0.86 (0.11)	1.01 (0.10)	.04

BMD, bone mineral density.

# Is Testosterone Deficiency Involved in the Etiology of Peyronie Disease?

Peyronie disease is common in urologic practices. At “Lunch With the Experts” with Dr Laurence A. Levine, several urologists agreed that they may see as many as 20 to 30 cases of Peyronie disease in a week, and sessions on Peyronie disease were well attended. The disorder is characterized by plaques and strands of dense fibrous tissue (scarring) of the tunica albuginea. Androgens play a key role in maintaining normal ultrastructure of erectile tissue, erectile function, and wound healing,<sup>51,61</sup> suggesting the possibility that testosterone deficiency might contribute to the pathogenesis of Peyronie disease. Two studies presented at AUA 2009 evaluated this hypothesis.

At a podium session, Sergio A Moreno, MD, presented results of a retrospective pilot study of 121 men with Peyronie disease (mean age, 54 y).<sup>62</sup> Only 10.6% recalled any penile trauma; 54.5% had ED, and 74.4% had testosterone deficiency (<300 ng/dL total testosterone [TT] and/or <1.5 ng/dL free testosterone [FT]). The severity of curvature was worse for those with low FT compared to those with normal levels. Dr Moreno speculated that Peyronie disease might result from reduced erectile rigidity, which leads to either injury or impaired tissue response to injury, involving reduced levels of the antifibrotic factor, nitric oxide (NO). One limitation of this study is use of a chi-square test to determine significance: Causality can only be determined by multivariate analysis. An abnormal FT level of <1.5 ng/dL suggests use of direct FT assay, which may be considered a limitation because of unreliability.

In a study presented by Renea Sturm, MD,<sup>63</sup> hypogonadism (TT <325 ng/dL) was significantly more common (76.5% vs 41.2%,  $P < .0001$ ) and the mean testosterone level was significantly lower (306 ng/dL vs 372 ng/dL,  $P < .05$ ) among 34 men with Peyronie disease-related ED compared with a control group with organic ED. Men with Peyronie disease thus appear to be at increased risk of hypogonadism versus men without Peyronie disease, and further studies are needed in larger patient populations, as well as in animal models of tunica albuginea injury. During the question-and-answer period following the presentation, Dr Abraham Morgentaler (co-investigator of the previous Peyronie disease study) commented that testosterone is unlikely to be the only cause but may be a contributing cause.

# No Extrusions or Infections With New Formulation of Implantable Testosterone Pellets

In a single-site US study of testosterone implants, Cavender et al<sup>64</sup> retrospectively analyzed data from 80 hypogonadal men (292 implant procedures; mean, 5.7 months between procedures). Both TT and FT levels improved between baseline and follow-up (mean, 58 d). No extrusions or infections were reported. The difference in extrusions and infection in this study compared with historical data

for European implants may be due to the manufacturing process, which in the newer US product results in a smaller pellet with a more regular surface and with no wool or cotton packaging. Patient satisfaction was high, with 86% of patients returning for their second or more implants. More research is needed to confirm the results of this small study.

# Testosterone for ED Not Responding to PDE5 Inhibitor Therapy

Addition of testosterone is known to improve responsiveness in some men with ED who do not respond to phosphodiesterase type 5 (PDE5) inhibitor therapy alone,<sup>65-67</sup> but the population of men likely to respond has not been defined. A European multicenter, double-blind, randomized trial<sup>68</sup> enrolled 173 men older than 45 years with a serum TT <4 ng/mL and/or a bioavailable T <1 ng/mL who had ED and did not respond to 4 weeks of daily tadalafil therapy. Many patients had only mild hypogonadism or low-normal testosterone levels. No overall

improvement was noted after 8 weeks of combined therapy. In subgroup analysis, however, hypogonadal men (TT <300 ng/dL) had significantly improved erectile function (Table 4). The lower the baseline TT or calculated FT, the lower the effect of tadalafil alone and the higher the effect of adding testosterone gel, confirming the testosterone dependence of responsiveness to PDE5 inhibitor therapy. The investigators cautioned that a 4-week follow-up may not be sufficient to detect all the men who may benefit. In addition, some of the changes were small and, although statistically significant, would be not be clinically relevant.

## Table 4. Testosterone Dependence of Responsiveness to PDE5 Inhibitor Therapy in Men With ED<sup>68</sup>

Baseline Testosterone	n	Increase in EFD Score			Increase in SEP3 Score, %		
		Testosterone Gel	Placebo	<i>P</i>	Testosterone Gel	Placebo	<i>P</i>
All	144	5.16	3.88	NS	36.4	30.8	NS
TT <400	93	5.22	3.92	NS	35.8	29.8	NS
TT <346	84	5.78	4.09	NS	38.3	28.1	NS
<b>TT &lt;300</b>	<b>61</b>	<b>6.18</b>	<b>2.33</b>	<b>0.027</b>	<b>33.1</b>	<b>13.4</b>	<b>0.038</b>
<b>TT &lt;231</b>	<b>36</b>	<b>5.65</b>	<b>1.13</b>	<b>0.035</b>	<b>32.2</b>	<b>9.4</b>	<b>0.065</b>
cFT Q3 <sup>a</sup>	109	5.83	3.88	0.073	36.9	27.8	NS
cFT Q2 <sup>b</sup>	73	6.75	2.47	0.055	34.2	22.3	NS

<sup>a</sup> <99.7 pg/mL.

<sup>b</sup> <65.2 pg/mL.

cFT, calculated free testosterone; ED, erectile dysfunction; EFD, erectile function domain; NS, not significant; PDE5, phosphodiesterase type 5; SEP3, sexual encounter profile question 3; TT, total testosterone.

# Clomiphene Citrate: An Alternative Treatment for Selected Hypogonadal Men

Previous studies have reported the effect of clomiphene citrate (CC) on testosterone/estrogen ratios within a hypogonadal population.<sup>69,70</sup> In a small retrospective study presented by Frederick L. Taylor, MD,<sup>71</sup> men were randomized to receive CC 50 mg every other day (n = 65) or testosterone gel (n = 39) 5 gm daily. The mean follow-up was 6.2 months for CC and 30.3 months for testosterone gel. Both groups had significant increases in serum TT from baseline to >550 ng/dL ( $P < .001$  for both). Men taking CC also had statistically significant increases in symptom scores on the ADAM questionnaire compared to men taking testosterone gel. This

small, nonrandomized, retrospective study had limited power, but the results warrant further investigation.

During “Lunch With the Experts” with Dr Levine, urologists at the table agreed that they are seeing increasingly more hypogonadal men who are only in their 40s. Dr Levine, who co-authored the study described above, discussed the off-label use of CC as an alternative to exogenous testosterone for younger men who want to preserve their fertility and for men with low-normal endogenous testosterone and low luteinizing hormone (LH); for all others, he prescribes exogenous testosterone. It should be noted that CC is not currently approved for this indication.

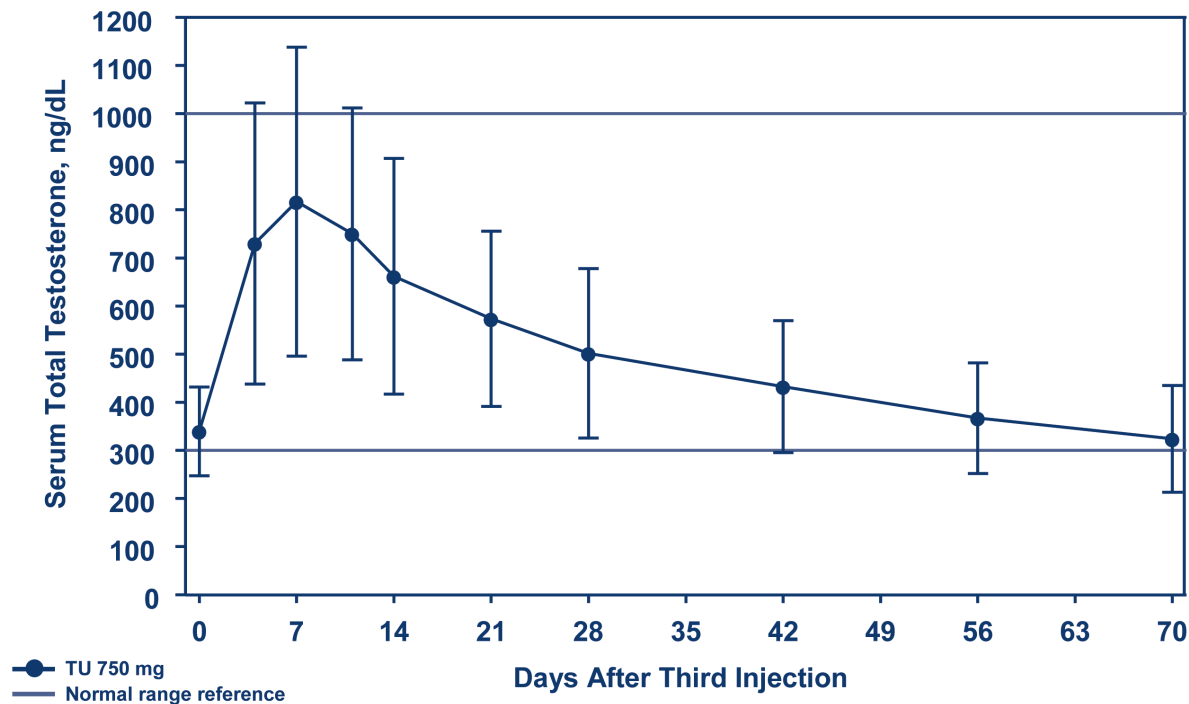
## Investigational New Products

### **Encouraging Results With Novel Long-acting Testosterone Undecanoate Injection**

At an industry-sponsored Satellite Breakfast Symposium, Dr Morgentaler presented an update on the safety, efficacy, and pharmacokinetics of TU, an IM injection with a long duration of action. In a phase 3 open-label trial (N=130),<sup>72</sup> TU 750 mg was safe and effective. The mean pretreatment testosterone level was 214.7 ng/dL. Mean testosterone concentrations reached physiologic levels by 4 days after first injection and remained in the physiologic

range throughout the 10-week dosing interval in 94% of subjects (Figure 4). TU did not cause supraphysiologic spikes of testosterone, and maximum testosterone concentrations remained within FDA standards (300-1000 ng/dL). Adverse events were nonserious and mild in severity. In response to a comment from the floor about the increase in lean mass for men who exercise while taking exogenous testosterone, Dr Morgentaler responded that, in his experience, most men add muscle mass and lose fat even if they do not exercise. He stated that the notable body composition changes are an important rationale for treatment. In another comment from the floor, Dr Aksam Yassin said that, in his practice in Germany, men are routinely started on long-acting IM TU.

Figure 4. Mean serum total testosterone after third injection of 750 mg TU at weeks 14 to 24.<sup>72</sup>



Reproduced with permission.  
TU, testosterone undecanoate.

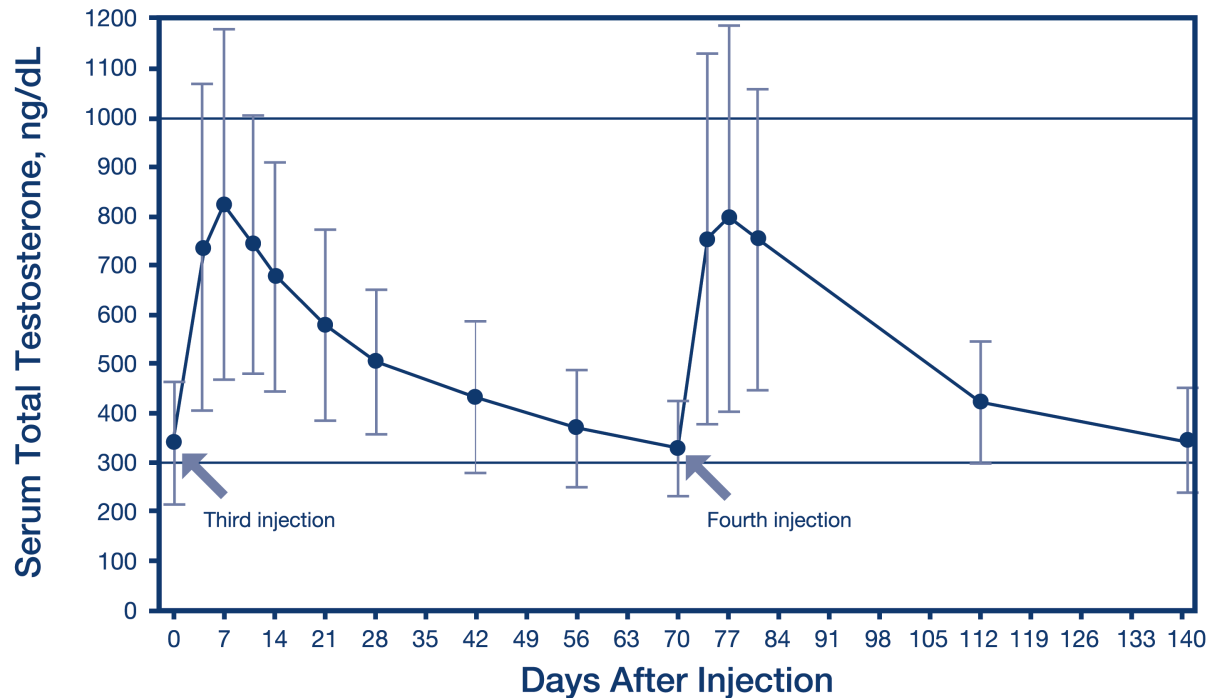
At a Moderated Poster session, Dr Morgentaler reported new, longer-term pharmacokinetic data on treatment with TU IM injection every 10 weeks for up to 21 months (extension phase, N=98).<sup>21</sup> Testosterone concentration profiles remained consistent, with nearly identical peaks and nadirs during subsequent intervals (Figure 5). Treatment was well tolerated. Average PSA levels increased from 1.0 ng/mL to 1.4 ng/mL over the entire 84-week observation period (mean PSA velocity, 0.25 ng/mL/y). Dr Morgentaler concluded that TU injection is an appealing new long-acting alternative treatment option for hypogonadal men.

In a podium presentation, Sompol Permpongkosol, MD, presented results from a small independent open-label study conducted in Thailand of TU 1000 mg in symptomatic hypogonadal men (TT <300 ng/dL).<sup>73</sup> Mean body mass index (BMI) of subjects was 25.71 kg/m<sup>2</sup> with numerous comorbidities (mean age, 60.3 y). TU was given on day 1, on day 42, and every 12 weeks thereafter for a mean duration of 51 weeks. One hundred eighteen men were investigated in this study. Total testosterone increased to the normal range in 93% of patients but did not remain stable after the first 3 injections. Waist circumference decreased 5.4 cm, lipids decreased slightly, AMS score decreased 2.9 points, IIEF-15 increased (particularly the erection score), and satisfaction increased in 73% of patients. No significant change was seen in BMI, PSA, International Prostate Symptom Score (IPSS), or International Index of Erectile Function (IIEF-5) score. No serious or unexpected adverse events were noted. Hematocrit increased 5% but did not result in treatment discontinuation. Dr Permpongkosol concluded that further studies with more patients and longer follow-up are warranted. It should be noted that the current TU dose being evaluated by the FDA for the US market is 750 mg.

### **A New Testosterone-in-Adhesive-Matrix Patch**

At a Moderated Poster session, J P Raynaud, MD, presented results of a randomized, open-label, European study<sup>74</sup> of a new matrix patch in which testosterone is dissolved in a non-alcoholic drug solvent, diethyltoluamide (N=224; mean age, 41.8 y). For the first year, 188 hypogonadal men received two patches applied every other day delivering testosterone 5 mg/d and 36 men received testosterone enanthate injection every 3 weeks. After 1 year, all men received the patch for an additional 4 years. The patch was well tolerated, with no change in lipid profiles or erythrocytes. Levels of PSA increased 0.2 ng/mL initially, then remained stable for the duration of the study. FT, DHT, and E<sub>2</sub> normalized. Total testosterone remained stable over time but was above the normal range in 85% of subjects. The protocol did not allow dosage alterations. Adhesiveness was at least 75% in ≥90% of the men. Symptom scores decreased and sexual function increased to reference values. Testosterone correlated significantly with sexual function changes. The patch was described as thin, transparent, comfortable, easy to use, and well accepted by patients. The primary disadvantage would appear to be local skin irritation and the need for alternate-day application.

Figure 5. Mean (SD) serum testosterone concentrations at steady state during 2 consecutive 10-week injection intervals with 750 mg testosterone undecanoate for 117 hypogonadal men with data available for pharmacokinetic analysis.<sup>21</sup>



Reproduced with permission.

# 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. *J Clin Endocrinol Metab.* 2006;91(6):1995-2010.
2. AACE Hypogonadism Task Force. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients—2002 update. *Endocrine Pract.* 2002;8(6):439-456.
3. Tenover JL. Male hormone replacement therapy including “andropause.” *Endocrinol Metab Clin North Am.* 1998;27(4):969-987.
4. Nieschlag E, Swerdloff R, Behre HM, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, and EAU recommendations. *Eur Urol.* 2005;48(1):1-4.
5. Kaufman JM, Vermeulen A. Declining gonadal function in elderly men. *Baillieres Clin Endocrinol Metab.* 1997;11(2):289-309.
6. Seftel A. Male hypogonadism. Part II: etiology, pathophysiology, and diagnosis [review]. *Int J Impot Res.* 2006;18:223-228.
7. 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.
8. Morley JE, Charlton E, Patrick P, et al. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism.* 2000;49(9):1239-1242.
9. Heinemann LA, Zimmermann T, Vermeulen A, Thiel C. A new ‘Aging Male’s Symptoms’ (AMS) scale. *Aging Male.* 1999;2:105-114.
10. Smith KW, Feldman HA, McKinlay JB. Construction and field validation of a self-administered screener for testosterone deficiency (hypogonadism) in ageing men. *Clin Endocrinol (Oxf).* 2000;53(6):703-711.
11. Araujo AB, McGraw SA, Connor M, et al. Development of a hypogonadism screener in men (abstract). Presented at: Sexual Medicine Society of North America Annual Meeting; October 16-18, 2008; Toronto, ON. Poster 18.
12. Wang C, Berman N, Longstreth JA, et al. Pharmacokinetics of transdermal testosterone gel in hypogonadal men: application of gel at one site versus four sites: a general clinical research center study. *J Clin Endocrinol Metab.* 2000;85(3):964-969.
13. Testosterone gel safety concerns prompt FDA to require label changes, medication guide [news release]. Silver Spring, MD: US Food and Drug Administration; May 7, 2009. <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149580.htm>. Accessed June 19, 2009.
14. Testopel [package insert]. Rye, NY: Bortor Pharmacal Co Inc; 2007.
15. Handelsman DJ, Mackey MA, Howe C, Turner L, Conway AJ. An analysis of testosterone implants for androgen replacement therapy. *Clin Endocrinol (Oxf).* 1997;47(3):311-316.
16. Jockenhövel F, Vogel E, Kreutzer M, Reinhardt W, Lederbogen S, Reinwein D. Pharmacokinetics and pharmacodynamics of subcutaneous testosterone implants in hypogonadal men. *Clin Endocrinol (Oxf).* 1996;45(1):61-71.
17. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring [review]. *N Engl J Med.* 2004;350(5):482-492.
18. Indevus announces submission of new drug application [news release]. MedicalNewsToday.com; August 29, 2007. <http://www.medicalnewstoday.com/printerfriendlynews.php?newsid=80880>. Accessed June 23, 2009.
19. Wang C, Swerdloff RS, Morgentaler A, et al. Effects of long-acting testosterone undecanoate injection on serum total testosterone and other sex hormones in the treatment of hypogonadism: results from a phase 3 clinical trial (poster). Presented at: Endocrine Society Annual Meeting; June 10-13, 2009; Washington, DC.
20. Morgentaler A, Dobs AS, Kaufman JM, et al. Safety, efficacy, and pharmacokinetics of testosterone undecanoate long-acting injection in the treatment of hypogonadism: results of a phase 3 clinical trial (poster). Presented at: Annual Meeting of the American Urological Association; May 17-22, 2008; Orlando, FL.
21. Morgentaler A, Kaufman JM, Shabsigh R, et al. First long acting testosterone undecanoate injection to treat male hypogonadism: 21 month safety and efficacy outcomes (abstract). *J Urol.* 2009;181(4 suppl):525-526. Abstract 1469.

# References

22. Morgentaler A, Kaufman JM, Dobs AS, et al. Long-acting testosterone undecanoate injection to treat male hypogonadism: 21-month safety and efficacy outcomes (poster). Presented at: Endocrine Society Annual Meeting; June 10-13, 2009; Washington, DC.
23. Morgentaler A, Miner M, Steidle C, et al. Improved male sexual function with a novel, long-acting testosterone undecanoate intramuscular injection (abstract). Presented at: Annual Meeting of Northeastern Section of American Urological Association; September 17-21, 2008; Santa Anna Pueblo, NM. Poster P57.
24. Hak AE, Wittman JCM, de Jong FH, Geerlings MI, Hofman A, Pols HAP. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam Study. *J Clin Endocrinol Metab*. 2002;87(8):3632-3639.
25. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a randomized, double-blind, placebo-controlled study. *Circulation*. 2000;102(16):1906-1911.
26. D'Amico AV, Denham JW, Crook J, et al. Influence of androgen suppression therapy for prostate cancer on the frequency and timing of fatal myocardial infarctions. *J Clin Oncol*. 2007;25(17):2420-2425.
27. Tivesten Å, Mellström D, Jutberger H, et al. Low serum testosterone and high serum estradiol associate with lower extremity peripheral arterial disease in elderly men: the MrOS Study in Sweden. *J Am Coll Cardiol*. 2007;50(11):1070-1076.
28. Khaw KT, Dowsett M, Folkard 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.
29. Laughlin GA, Barrett-Conner E, Bergstrom J. Low serum testosterone and mortality in older men. *J Clin Endocrinol Metab*. 2008;93(1):68-75.
30. Morgentaler A, Rhoden EL. Prevalence of prostate cancer among hypogonadal men with prostate-specific antigen of 4.0 ng/mL or less. *Urology*. 2006;68(6):1263-1267.
31. 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(10):2351-2361.
32. Morgentaler A. Testosterone and prostate cancer: an historical perspective on a modern myth. *Eur Urol*. 2006;50(5):935-939.
33. Endogenous Hormones and Prostate Cancer Collaborative Group, Roddam AW, Allen NE, Appleby P, Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *J Natl Cancer Inst*. 2008;100(3):170-183.
34. Coviello AD, Kaplan B, Lakshman KM, Chen T, Singh AB, Bhasin S. Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. *J Clin Endocrinol Metab*. 2008;93(3):914-919.
35. Gonzales GF, Gasco M, Tapia V, Gonzales-Castaneda C. High serum testosterone levels are associated to excessive erythrocytosis of chronic mountain sickness in men. *Am J Physiol Endocrinol Metab*. 2009 Mar 24 [Epub ahead of print].
36. Matsumoto AM, Sandblom RE, Schoene RB, et al. Testosterone replacement in hypogonadal men: effects on obstructive sleep apnoea, respiratory drives, and sleep. *Clin Endocrinol*. 1985;22(6):713-721.
37. 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.
38. Prout GR Jr, Brewer WR. Response of men with advanced prostatic carcinoma to exogenous administration of testosterone. *Cancer*. 1967;20:1871-1878.
39. Fowler JE Jr, Whitmore WF Jr. The response of metastatic adenocarcinoma of the prostate to exogenous testosterone. *J Urol*. 1981;126(3):372-375.
40. Morgentaler A, Traish AM. Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. *Eur Urol*. 2009;55(2):310-321.
41. Morgentaler A. Two years of testosterone therapy associated with decline in prostate-specific antigen in a man with untreated prostate cancer. *J Sex Med*. 2009;6(2):574-577.
42. Shores MM, Matsumoto AM, Sloan KL, Kivlahan DR. Low serum testosterone and mortality in male veterans. *Arch Intern Med*. 2006;166(15):1660-1665.

# References

43. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol*. 2006;24(27):4448-4456.
44. Khera M, Grober ED, Najari B, et al. Testosterone replacement therapy following radical prostatectomy. *J Sex Med*. 2009;6(4):1165-1170.
45. Kaufman JM, Graydon RJ. Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. *J Urol*. 2004;172(3):920-922.
46. Sarosdy MF. Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. *Cancer*. 2007;109(3):536-541.
47. Morgentaler A. Testosterone replacement therapy and prostate cancer. *Urol Clin North Am*. 2007;34(4):555-563, vii.
48. Daniels NA, Nielson CM, Hoffman AR, Bauer DC. Sex hormones and prostate cancer risk (abstract). *J Urol*. 2009;181(4 suppl):167. Abstract 466.
49. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. *J Natl Cancer Inst*. 1996;88(16):1118-1126.
50. Zitzman M, Brune M, Nieschlag E. Vascular reactivity in hypogonadal men is reduced by androgen substitution. *J Clin Endocrinol Metab*. 2002;87(11):5030-5037.
51. Foresta C, Caretta N, Lana A, et al. Reduced number of circulating endothelial progenitor cells in hypogonadal men. *J Clin Endocrinol Metab*. 2006;91(11):4599-4602.
52. De Pergola G, Pannaciuoli N, Ciccone M, Tartagni M, Rizzon P, Giorgino R. Free testosterone plasma levels are negatively associated with the intima-media thickness of the common carotid artery in overweight and obese glucose-tolerant young adult men. *Int J Obes Relat Metab Disord*. 2003;27(7):803-807.
53. Tsai HK, D'Amico AV, Sadetsky N, Chen MH, Carroll PR. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *J Natl Cancer Inst*. 2007;99:1516-1524.
54. Berookhim BM, Bar-Chama NC, McLaughlin MA, et al. Male hypogonadism and coronary calcium scores in a subset of participants in the World Trade Center medical monitoring and treatment program (abstract). *J Urol*. 2009;181(4 suppl):329. Abstract 922.
55. Möhlenkamp S, Lehmann N, Schmermund A, et al. Prognostic value of extensive coronary calcium quantities in symptomatic males—a 5-year follow-up study. *Eur Heart J*. 2003;24:845-854.
56. Budoff MJ, Gul KM. Expert review on coronary calcium [review]. *Vasc Health Risk Management*. 2008;4(2):315-324.
57. Mohammed O, Colen J, Lipshultz L, Khera M. Association between endothelial function assessment and hypogonadal status in patients presenting with erectile dysfunction (abstract). *J Urol*. 2009;181(4 suppl):367. Abstract 1025.
58. Benito M, Gomberg B, Wehrli FW, et al. Deterioration of trabecular architecture in hypogonadal men. *J Clin Endocrinol Metab*. 2003;88(4):1497-1502.
59. Donaldson LJ, Cook A, Thomson RG. Incidence of fractures in a geographically defined population. *J Epidemiol Comm Health*. 1990;44:241-245.
60. Seo JT, Kim TH, Choe JH, Lee JS. The influence of testosterone replacement therapy on bone mineral density in patients with Klinefelter's syndrome (abstract). *J Urol*. 2009;181(4 suppl):366-367. Abstract 1023.
61. Traish AM. Androgens play a pivotal role in maintaining penile tissue architecture and erection: a mini review. *J Androl*. 2008 Sep 18 [Epub ahead of print].
62. Moreno SA, Morgentaler A. Testosterone deficiency as a possible etiologic factor in Peyronie's disease (abstract). *J Urol*. 2009;181(4 suppl):278. Abstract 778.
63. Sturm R, Rumohr JA, Lipshultz LI, Mohamed O, Khera M. Increased incidence of hypogonadism in patients with a novel diagnosis of Peyronie's disease as compared to organic erectile dysfunction. *J Urol*. 2009;181(4 suppl):278-279. Abstract 779.
64. Cavender RK, Fairall M, Vorhees WF. Subcutaneous testosterone pellet implant therapy in the United States for men with testosterone deficiency syndrome: a single-site retrospective safety and efficacy study (abstract). *J Urol*. 2009;181(4 suppl):488. Abstract 1366.
65. Greco EA, Spera G, Aversa A. Combining testosterone and PDE5 inhibitors in erectile dysfunction; basic rationale and clinical evidences. *Eur Urol*. 2006;50:940-947.

# References

66. Shabsigh R, Rajfer J, Aversa A, et al. The evolving role of testosterone in the treatment of erectile dysfunction [review]. *Int J Clin Pract.* 2006;60(9):1087-1092.
67. McMahon CN, Smith CJ, Shabsigh R. Treating erectile dysfunction when PDE5 inhibitors fail [review]. *BMJ.* 2006;332(7541):589-592.
68. Buvat J, Montorsi F, Cuzin B, Meuleman E, Yassin A, Dean J. From which serum testosterone level should we add testosterone therapy to men with erectile dysfunction not responding to PDE5 inhibitors alone? A double blind placebo-controlled trial of testosterone gel addition to men not responding to tadalafil once a day alone (abstract). *J Urol.* 2009;181(4 suppl):488. Abstract 1367.
69. Shabsigh A, Kang Y, Shabsigh R, et al. Clomiphene citrate effects on testosterone/estrogen ratio in male hypogonadism. *J Sex Med.* 2005;2(5):716-721.
70. Whitten SJ, Nangia AK, Kolettis PN. Select patients with hypogonadotropic hypogonadism may respond to treatment with clomiphene citrate. *Fertil Steril.* 2006;86(6):1664-1668.
71. Taylor FL, Levine LA. Clomiphene citrate versus testosterone gel replacement therapy for hypogonadism: biochemical and clinical efficacy and treatment cost (abstract). *J Urol.* 2009;181(4 suppl):488-489. Abstract 1368.
72. 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.
73. Permpongkosol S, Talubsri R. Long-acting intramuscular testosterone undecanoate for the treatment of 118 late-onset hypogonadism in males (abstract). *J Urol.* 2009;181(4 suppl):489. Abstract 1369.
74. Raynaud JP, Legros JJ, Rollet J, Fiet J. Efficacy and safety of a new testosterone-in-adhesive matrix patch applied every two days for five years to hypogonadal men (abstract). *J Urol.* 2009;181(4 suppl):729. Abstract 2012.

**For additional educational activities, please visit**

**TU** TestosteroneUpdate®  
Collaborative for Improved Clinical Outcomes in Hypogonadism  
[www.TestosteroneUpdate.org](http://www.TestosteroneUpdate.org)

**Primary**Perspective   
Continuing Medical Education for the Primary Care Clinician

---

[www.PrimaryPerspective.org](http://www.PrimaryPerspective.org)