Proceedings From the TU 1st Annual Conference on
Improving Clinical Outcomes in Hypogonadism

1 Letter From the Co-Chairs
Glenn R. Cunningham, MD, and
Ridwan Shabsigh, MD

2 CME Accreditation Information

4 Introduction

4 Epidemiology of Hypogonadism
Glenn R. Cunningham, MD

5 Diagnosis and Management of
Hypogonadism and Associated
Chronic Comorbid Conditions
From the Primary Care Perspective
Richard Sadovsky, MD

7 Laboratory Diagnosis of
Hypogonadism:
The Clinical Imperative
Shalender Bhasin, MD

8 Hypogonadism Treatment
Considerations, Monitoring,
and Follow-up
Adrian S. Dobs, MD, MHS

10 Novel Testosterone Formulations and
Dosing: Potential Impact on Treatment
and Outcomes
Ajay Nehra, MD

12 Testosterone Therapy and the Prostate:
Evaluating the Evidence
Leonard S. Marks, MD

13 Testosterone and the Prostate:
What Is the Relationship?
Abraham Morgentaler, MD

14 Monitoring and Treatment After
Prostatectomy or Brachytherapy
E. David Crawford, MD

16 Conclusion

17 References
Dear Colleague:

Hypogonadism affects at least 4 million men in the United States, and its prevalence increases with age. Low testosterone levels have been associated with insulin resistance, metabolic syndrome, diabetes, and other chronic comorbid conditions. However, hypogonadism is generally underdiagnosed and undertreated.

Physicians treating patients with male hypogonadism joined key opinion leaders for the TU 1st Annual Conference on Improving Clinical Outcomes in Hypogonadism held November 3, 2007, at the American Conference Center in New York, New York, to discuss therapy options and clinical considerations for treating patients with low testosterone. This CME-certified paper was developed through the efforts of the presenting and contributing distinguished faculty.

Faculty members addressed issues facing physicians who treat patients diagnosed with hypogonadism, such as the concern surrounding the association between testosterone therapy and prostate cancer. In addition, the faculty offered suggestions to help physicians make more informed treatment decisions regarding their patients with hypogonadism.

This activity has been approved for 1.5 AMA PRA Category 1 Credits™.

We hope that you find the information in this paper useful when treating your hypogonadal male patients.

Sincerely,

Glenn R. Cunningham, MD
Co-Chairperson

Ridwan Shabsigh, MD
Co-Chairperson

ACKNOWLEDGMENTS

The faculty would like to thank the following physicians who participated in the TU 1st Annual Conference on Improving Clinical Outcomes in Hypogonadism, which convened in New York, New York, on November 3, 2007: Culley C. Carson III, MD, Frances J. Hayes, MD, Joel M. Kaufman, MD, Alvin M. Matsumoto, MD, Kevin M. Slawin, MD, Ronald S. Swerdloff, MD, Abdulmaged M. Traish, PhD, and Christina Wang, MD.
This activity was developed for physicians and other clinicians who are interested in treating patients with male hypogonadism.

Hypogonadism affects several million men in the United States, its prevalence increases with age, and it is underdiagnosed and undertreated. Reasons for underdiagnosis and undertreatment are numerous. First, signs and symptoms of low testosterone are often subtle and nonspecific. Second, a consensus on the definition of low testosterone has not been established. Many commercially available assays for the measurement of testosterone levels have not been standardized, resulting in considerable variability among laboratories in reference values for identifying low testosterone levels.

It is important to understand these challenges to optimize patient outcomes with the benefits of testosterone therapy. Additionally, low testosterone has been associated with insulin resistance, metabolic syndrome, diabetes, and other chronic comorbid conditions. A recent study reports that testosterone therapy improved insulin resistance and glycemic control in hypogonadal men with type 2 diabetes. Unfortunately, few large randomized clinical trials adequately address prostate safety during long-term testosterone therapy. Many testosterone therapies are currently marketed, but a safe, efficacious formulation that more closely mimics endogenous testosterone is still needed. This conference presents data and expert opinion to address the underdiagnosis and undertreatment of hypogonadism and to provide clinicians with strategies for treating patients with hypogonadism, including testosterone therapy.

Upon completion of this activity, participants should be better able to:
- Analyze the important clinical issues pertaining to treatment options for patients with hypogonadism
- Discuss the epidemiology of hypogonadism and how to identify, test for, and diagnose the condition
- Initiate and monitor testosterone therapy for optimal and safe treatment
- Describe current and novel testosterone therapy options
- Explain prostate disease risk and appropriate testosterone treatment monitoring parameters for individual patients

INTENDED AUDIENCE

This activity was developed for physicians and other clinicians who are interested in treating patients with male hypogonadism.

STATEMENT OF NEED

Hypogonadism affects several million men in the United States, its prevalence increases with age, and it is underdiagnosed and undertreated. Reasons for underdiagnosis and undertreatment are numerous. First, signs and symptoms of low testosterone are often subtle and nonspecific. Second, a consensus on the definition of low testosterone has not been established. Many commercially available assays for the measurement of testosterone levels have not been standardized, resulting in considerable variability among laboratories in reference values for identifying low testosterone levels.

It is important to understand these challenges to optimize patient outcomes with the benefits of testosterone therapy. Additionally, low testosterone has been associated with insulin resistance, metabolic syndrome, diabetes, and other chronic comorbid conditions. A recent study reports that testosterone therapy improved insulin resistance and glycemic control in hypogonadal men with type 2 diabetes. Unfortunately, few large randomized clinical trials adequately address prostate safety during long-term testosterone therapy. Many testosterone therapies are currently marketed, but a safe, efficacious formulation that more closely mimics endogenous testosterone is still needed. This conference presents data and expert opinion to address the underdiagnosis and undertreatment of hypogonadism and to provide clinicians with strategies for treating patients with hypogonadism, including testosterone therapy.

LEARNING OBJECTIVES

Upon completion of this activity, participants should be better able to:
- Analyze the important clinical issues pertaining to treatment options for patients with hypogonadism
- Discuss the epidemiology of hypogonadism and how to identify, test for, and diagnose the condition
- Initiate and monitor testosterone therapy for optimal and safe treatment
- Describe current and novel testosterone therapy options
- Explain prostate disease risk and appropriate testosterone treatment monitoring parameters for individual patients

CO-CHAIRPERSONS

Glenn R. Cunningham, MD
Professor of Medicine and Molecular & Cellular Biology
Baylor College of Medicine
Medical Director, St. Luke's Episcopal Hospital–Baylor College of Medicine Diabetes Program
Houston, Texas

Ridwan Shabsigh, MD
Director, Division of Urology
Maimonides Medical Center
Brooklyn, New York
Professor of Urology
College of Physicians & Surgeons of Columbia University
New York, New York

FACULTY

Shalender Bhasin, MD
Professor of Medicine
Boston University School of Medicine
Chief, Section of Endocrinology, Diabetes, and Nutrition
Boston Medical Center
Boston, Massachusetts

E. David Crawford, MD
Professor of Surgery, Urology, and Radiation Oncology
Head, Urologic Oncology
Endowed Chair in Urologic Oncology
University of Colorado Health Sciences Center
Aurora, Colorado

Adrian S. Dobs, MD, MHS
Professor of Medicine and Oncology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Leonard S. Marks, MD
Clinical Professor
Department of Urology
Geffen School of Medicine
University of California at Los Angeles (UCLA)
Los Angeles, California
Medical Director
Urological Sciences Research Foundation
Culver City, California

Abraham Morgentaler, MD
Director, Men’s Health Boston
Beth Israel Deaconess Medical Center
Associate Clinical Professor
Urologic Surgery
Harvard Medical School
Boston, Massachusetts

Ajay Nehra, MD
Professor of Urology
Department of Urology
Mayo Medical School
Mayo Clinic
Rochester, Minnesota

Richard Sadowsky, MD
Associate Professor of Family Practice
State University of New York
Health Science Center at Brooklyn
Brooklyn, New York

REFERENCES

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Annenberg Center for Health Sciences at Eisenhower and CogniMed Inc. The Annenberg Center is accredited by the ACCME to provide continuing medical education for physicians.

The Annenberg Center designates this educational activity for a maximum of 1.5 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The Annenberg Center for Health Sciences is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s Commission on Accreditation.

A maximum of 1.5 contact hours may be earned for successful completion of this activity.

A&A accepts Prescribed credit from AAFP and Category 1 CME credit for the PRA from organizations accredited by ACCME.

Course meets the qualifications for 1.5 hours of continuing education for MFTs and/or LCSWs as required by the California Board of Behavioral Sciences. Provider #PCE2048.

This program is cosponsored by the Annenberg Center for Health Sciences at Eisenhower and CogniMed Inc. The Annenberg Center is approved by the American Psychological Association to sponsor continuing education for psychologists. The Annenberg Center maintains responsibility for this program and its content. This activity is designated for 1.5 hours of credit.

There is no charge for this activity. Statements of Credit will be provided by mail following activity participation and upon completion and return of the evaluation form to TestosteroneUpdate, c/o CogniMed Inc., 70 South Orange Avenue, Suite 200, Livingston, NJ 07039, or by fax to 877-403-5765. Please allow 4 to 6 weeks for the delivery of your statement.

It is the policy of the Annenberg Center to ensure fair balance, independence, objectivity, and scientific rigor in all programming. All faculty and planners participating in sponsored programs are expected to identify and reference off-label product use and disclose any significant relationship with those supporting the activity or any others whose products or services are discussed.

In accordance with the Accreditation Council for Continuing Medical Education Standards, parallel documents from other accrediting bodies, and Annenberg Center policy, the following disclosures have been made:

Glenn R. Cunningham, MD, reports that he has received speakers bureau honoraria from Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc; and Solvay S.A.; consultant honoraria from Indevus Pharmaceuticals, Inc., and Solvay S.A.; advisor honoraria from Columbia Laboratories, Inc., and Indevus Pharmaceuticals, Inc.; and investigator grants from Ardana Bioscience; Ascend Therapeutics, Inc.; Columbia Laboratories, Inc.; Sanofi-Aventis; and Solvay S.A. He reports that this activity will include discussion of investigational or unlabeled use of a product. Dr Cunningham has no identified conflicts of interest.

Ridwan Shabsigh, MD, reports that he has received speakers bureau honoraria from American Medical Systems; Auxilium Pharmaceuticals, Inc.; Bayer Pharmaceuticals Corp.; Eli Lilly and Company; and Schering-Plough Corporation; and consultant honoraria from American Medical Systems; Bayer Pharmaceuticals Corp.; Boehringer Ingelheim; Eli Lilly and Company; Indevus Pharmaceuticals, Inc.; Johnson & Johnson; Pfizer Inc; and Schering-Plough Corporation. He also reports that this activity will include discussion of investigational or unlabeled use of a product. Dr Shabsigh has no identified conflicts of interest.

Shalender Bhasin, MD, reports that he does not have any relevant financial relationships with any commercial interests. He also reports that his presentation will not include discussion of any investigational or unlabeled use of a product. Dr Bhasin has no identified conflicts of interest.

E. David Crawford, MD, reports that he is a speaker/lecturer for AstraZeneca; Aventis; GlaxoSmithKline; Lilly; Merck & Co.; Oncura; and TAP Pharmaceutical Products Inc. He serves as research support/scientific trials for the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Cancer Center. He is also an investigator for and board member of the Southwest Oncology Group.

Adrian S. Dobs, MD, MHS, has received research support from Indevus Pharmaceuticals, Inc., and Solvay S.A.

Leonard S. Marks, MD, reports that he does not have any relevant financial relationships with any commercial interests. He also reports that his presentation will not include discussion of any investigational or unlabeled use of a product. Dr Marks has no identified conflicts of interest.

Abraham Morgentaler, MD, serves as research support for Indevus Pharmaceuticals, Inc.; Lilly; and Solvay S.A. He is also on the speakers bureaus of Auxilium Pharmaceuticals, Inc; Lilly; Pfizer Inc.; and Solvay S.A. He reports that his presentation will include discussion of commercial product or services.

Ajay Nehra, MD, serves as a consultant for American Medical Systems; Bayer Pharmaceuticals Corp.; Coloplast; Indevus Pharmaceuticals, Inc; and Pfizer Inc. He reports that his presentation will include discussion of commercial product or services. He also reports that he does not intend to reference unlabeled/unapproved uses of drugs or products in his presentation.

Richard Sadovsky, MD, is a consultant for Lilly and Pfizer Inc and serves on the speakers bureau of Pfizer Inc.

The ideas and opinions presented in this educational activity are those of the faculty and do not necessarily reflect the views of the Annenberg Center and/or its agents. As in all educational activities, we encourage the practitioners to use their own judgment in treating and addressing the needs of each individual patient, taking into account that patient’s unique clinical situation. The Annenberg Center disclaims all liability and cannot be held responsible for any problems that may arise from participating in this activity or following treatment recommendations presented.

This activity is supported by an independent educational grant from Indevus Pharmaceuticals, Inc.

The estimated time to complete the activity is 1.5 hours.

This activity was originally released May 30, 2008, and is eligible for credit through May 30, 2009.

This piece is based on presentations from faculty members and was written by a medical writer. Faculty have final editorial control for the piece.
INTRODUCTION

Hypogonadism is defined as a clinical condition in which low levels of serum testosterone are associated with signs and symptoms that include diminished libido and sense of vitality, erectile dysfunction (ED), reduced muscle mass and bone density, depression, and anemia. Hypogonadism is a highly prevalent condition, affecting 2 to 4 million men in the United States, and is underdiagnosed and undertreated despite available effective therapies.

Besides the well-known signs and symptoms of hypogonadism, low levels of testosterone have been associated with insulin resistance, metabolic syndrome, diabetes, and other chronic comorbid conditions.

One of the challenges clinicians face when treating men with hypogonadism is lack of awareness about how to assess and diagnose this condition. Signs and symptoms of hypogonadism are affected by age and comorbid conditions, and there is no consensus on a definition of “low testosterone” levels applicable for clinical purposes. Testosterone assays have varying reference ranges, which may lead to conflicting results.

Furthermore, there are no randomized controlled trials addressing prostate safety during long-term testosterone therapy. To improve patient outcomes, clinicians must overcome these challenges with regard to male hypogonadism.

Recognizing the importance of awareness and education around hypogonadism, clinicians from the fields of primary care, urology, and endocrinology convened in New York, New York, on November 3, 2007, to present the TU 1st Annual Conference on Improving Clinical Outcomes in Hypogonadism. Participants discussed facets of awareness, epidemiology, testing, and diagnosis of hypogonadism; reviewing the initiation and monitoring of testosterone therapy in an effective manner; describing current and novel testosterone therapy options; and explaining the relationship of testosterone to prostate disease.

EPIDEMIOLOGY OF HYPOGONADISM

Glenn R. Cunningham, MD

The Endocrine Society has defined hypogonadism in men as “a clinical syndrome that results from failure of the testes to produce physiologic levels of testosterone (androgen deficiency) and the normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-gonadal axis.” Hypogonadism can be primary, secondary, or mixed, as illustrated in Table 1. Young men who are androgen deficient because of abnormalities of the testes, pituitary gland, or hypothalamus present with signs and symptoms such as decreased bone mineral density (BMD), cognition, memory, mood, sexual desire and function, strength, and energy. Late-onset hypogonadism results in similar age-related changes due to decreased levels of testosterone.

Several cross-sectional studies have demonstrated that testosterone levels decrease as men age. The Baltimore Longitudinal Study of Aging (N=890) demonstrated significant, independent longitudinal effects of age on both testosterone and free testosterone index (serum testosterone divided by sex hormone-binding globulin [SHBG]). In men aged 40 to 79 years, the percentage of men with hypogonadism defined by total testosterone or free testosterone index increased progressively after age 50. A significant proportion of men older than 60 years had low serum testosterone concentrations that would define them as hypogonadal (Figure 1).

Similar data were obtained from the Massachusetts Male Aging Study (MMAS), a 10-year prospective observational survey. Results of this study compared cross-sectional data with longitudinal data and found that, in addition to declining testosterone levels, chronic diseases were more likely to develop as men age. Testosterone levels were lower in men followed longitudinally than in cross-sectional studies of similarly aged men. This is because the former develop medical conditions that lower total and free testosterone levels.

In a study by Araujo and colleagues, chronic diseases occurred at a greater rate in men with low free testosterone, compared with men with low total testosterone, because of a sharp rise in the proportion of men with elevated SHBG. Age-specific prevalence of symptomatic androgen deficiency was significantly greater in the

Table 1. Classification of Hypogonadism

<table>
<thead>
<tr>
<th>Primary&lt;sup&gt;5,11&lt;/sup&gt;</th>
<th>Secondary&lt;sup&gt;6&lt;/sup&gt;</th>
<th>Mixed&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testicular causes</td>
<td>Hypothalamic causes</td>
<td>Pituitary causes</td>
</tr>
<tr>
<td>Klinefelter syndrome</td>
<td>Kallmann syndrome</td>
<td>Hypogonitalism</td>
</tr>
<tr>
<td>Orchiectomy</td>
<td>Constitutional delay in growth and development</td>
<td>Pituitary tumors</td>
</tr>
<tr>
<td>Congenital or acquired anorchia</td>
<td>Chronic illnesses</td>
<td>Genetic hypogonadism</td>
</tr>
<tr>
<td>Testicular tumors</td>
<td>Sleep apnea</td>
<td>Hypogonitalism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>HPG, hypothalamic-pituitary-gonadal.
oldest age group (70 to 79 years) compared with all other groups (pairwise comparisons, \( P < .05 \)). The authors estimated that, by the year 2025, 6.5 million American men aged 30 to 79 years will suffer from symptomatic androgen deficiency, which is an increase of 38% from 2000 population estimates.

The Hypogonadism in Males study was undertaken to determine the prevalence of total testosterone <300 ng/dL in men 45 years of age or older who present to primary care clinicians. Of the 2162 patients, 836 were hypogonadal (~10% were receiving treatment). The data also showed that untreated low testosterone levels were associated with obesity, diabetes, hypertension, rheumatoid arthritis, hyperlipidemia, osteoporosis, and asthma or chronic obstructive pulmonary disease.\(^{17}\)

Taken together, these data show that hypogonadism is common, and its prevalence increases as men age. As the population of older men continues to increase, so will the number of hypogonadal men increase.

**Testosterone and comorbid conditions**

Testosterone deficiency and the aging process have been linked to the development or exacerbation of other chronic conditions. Low levels of total testosterone (<200 ng/dL) are associated with an increased risk of osteoporosis of the hip (\( P = .003 \)). Further, individuals with low serum estradiol (<10 pg/mL) and low bioavailable estradiol are at increased risk for osteoporosis of the hip (\( P < .0001 \) for both).\(^{18}\) Estradiol levels are usually directly proportional to testosterone levels.

In addition to osteoporosis, hypogonadism is a predictor of the development of diabetes and metabolic syndrome. Laaksonen and colleagues studied this association between low levels of testosterone in 702 middle-aged men without diabetes or metabolic syndrome (Figure 2).\(^{19}\) Patients were followed for 11 years, by which time 147 men had metabolic syndrome, as defined by National Cholesterol Education Program criteria, and 57 men had diabetes. After adjusting for age, men who initially had total testosterone, calculated free testosterone, and SHBG levels in the lowest quartile were at increased risk for metabolic syndrome (odds ratio [OR], 2.3, 1.7, and 2.8, respectively) and diabetes (OR, 2.3, 1.7, and 4.3, respectively). The authors concluded that low total testosterone and SHBG levels independently predict future development of metabolic syndrome and diabetes in middle-aged men independent of other factors related to insulin resistance and therefore should be used as markers for these conditions.

Finally, the association between low testosterone and chronic conditions has been linked to higher mortality. The Rancho Bernardo Study, a population-based prospective study, demonstrated that low testosterone levels (<241 ng/dL) in older men (median age, 73.6 years) were associated with increased mortality over time (N = 794), independent of multiple risk factors.\(^{20}\) In a retrospective study of male veterans (N = 858), low testosterone levels (<250 ng/dL) were associated with a significant increase in mortality (\( P < .001 \)) even after adjusting for age, medical morbidity, and other clinical covariates.\(^{21}\)

**Table 2. Effects of Testosterone and Its Metabolites on Target Organs**

<table>
<thead>
<tr>
<th>Target Organs and Systems in the Body</th>
<th>Physiologic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>↑ libido, energy, well-being, spatial cognition</td>
</tr>
<tr>
<td>Hypothalamus/pituitary</td>
<td>↓ GnRH, LH, FSH; ↑ GH</td>
</tr>
<tr>
<td>Larynx</td>
<td>Lowers voice</td>
</tr>
<tr>
<td>Breast</td>
<td>↑ size</td>
</tr>
<tr>
<td>Liver</td>
<td>↓ SHBG, HDL</td>
</tr>
<tr>
<td>Kidney</td>
<td>↑ erythropoietin</td>
</tr>
<tr>
<td>Genitals</td>
<td>↓ development, ↓ sperm, erections</td>
</tr>
<tr>
<td>Prostate</td>
<td>↑ size, secretions</td>
</tr>
<tr>
<td>Skin</td>
<td>↑ facial/body hair, sadem production</td>
</tr>
<tr>
<td>Bone</td>
<td>↑ formation</td>
</tr>
<tr>
<td>Muscle</td>
<td>↑ lean mass, strength</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>↑ lipolysis, ↓ abdominal fat</td>
</tr>
<tr>
<td>Blood</td>
<td>↑ hematocrit</td>
</tr>
<tr>
<td>Immune system</td>
<td>↓ auto-antibody production</td>
</tr>
</tbody>
</table>

**Figure 2. Low Levels of Total Testosterone Predict the Development of Metabolic Syndrome and Diabetes: Population-Based Cohort Study—11-Year Follow-up**

**Table 2. Effects of Testosterone and Its Metabolites on Target Organs**

<table>
<thead>
<tr>
<th>Target Organs and Systems in the Body</th>
<th>Physiologic Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>↑ libido, energy, well-being, spatial cognition</td>
</tr>
<tr>
<td>Hypothalamus/pituitary</td>
<td>↓ GnRH, LH, FSH; ↑ GH</td>
</tr>
<tr>
<td>Larynx</td>
<td>Lowers voice</td>
</tr>
<tr>
<td>Breast</td>
<td>↑ size</td>
</tr>
<tr>
<td>Liver</td>
<td>↓ SHBG, HDL</td>
</tr>
<tr>
<td>Kidney</td>
<td>↑ erythropoietin</td>
</tr>
<tr>
<td>Genitals</td>
<td>↓ development, ↓ sperm, erections</td>
</tr>
<tr>
<td>Prostate</td>
<td>↑ size, secretions</td>
</tr>
<tr>
<td>Skin</td>
<td>↑ facial/body hair, sadem production</td>
</tr>
<tr>
<td>Bone</td>
<td>↑ formation</td>
</tr>
<tr>
<td>Muscle</td>
<td>↑ lean mass, strength</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>↑ lipolysis, ↓ abdominal fat</td>
</tr>
<tr>
<td>Blood</td>
<td>↑ hematocrit</td>
</tr>
<tr>
<td>Immune system</td>
<td>↓ auto-antibody production</td>
</tr>
</tbody>
</table>

BMD, bone mineral density; CNS, central nervous system; E2, estradiol; FSH, follicle-stimulating hormone; GH, growth hormone; GnRH, gonadotropin-releasing hormone; HDL, high-density lipoprotein; LH, luteinizing hormone; SHBG, sex hormone-binding globulin.\(^{12}\)

**DISCUSSION**

Richard Sadovsky, MD

To address hypogonadism from a primary care perspective, it is important to recognize a few key facts about testosterone, including its production, metabolites, physiologic effects, and clinical manifestations; drugs that may cause hypogonadism; and reasons to screen for the condition.

Testosterone and its metabolites have many physiologic effects on several target organs. Most relevant are the effects on the central nervous system, bone, muscle, and blood. However, as illustrated by Table 2, a multitude of organs are affected by a man’s androgen status.\(^{5,11,17}\) Clinical manifestations of low testosterone include physical, metabolic, psychological, and sexual changes, as outlined in Table 3.

Testosterone is the major androgen in men, in terms of both concentration and activity. In healthy men, the testes secrete...
between 4 and 9 mg of testosterone daily, most of which is synthesized from cholesterol by Leydig cells. Testosterone is metabolized by peripheral tissue into dihydrotestosterone (DHT) and estradiol through \( \alpha \) reductase and aromatase, respectively. DHT is a ligand for androgen receptors and subsequently affects sexual and physical characteristics. In the male, estradiol is bound to estrogen receptors, especially those that affect bone density.22

According to the Endocrine Society Guidelines, a man should be screened for hypogonadism if he presents with any of the following5:

- Sellar mass, radiation to or diseases of the sella
- Medications that affect testosterone production or metabolism
- Weight loss associated with human immunodeficiency virus (HIV)
- End-stage renal disease or maintenance hemodialysis
- Moderate to severe chronic obstructive lung disease
- Infertility
- Osteoporosis or low-trauma fracture (particularly in younger men)
- Type 2 diabetes or metabolic syndrome

Further, any older man with significant symptoms consistent with testosterone deficiency should be screened.5

A cross-sectional study (N=746) in a urology center by Rhoden and colleagues evaluated the relationship between diabetes and levels of serum free and total testosterone.23 The mean age of patients was 55.2 years (range, 15-90 years), and subnormal levels were defined as <12.4 pg/mL for free testosterone and <400 ng/dL for total testosterone. Serum total testosterone and free testosterone levels were subnormal, 34% and 46%, respectively, in men with diabetes, and 23% and 24%, respectively, in men without diabetes. Men with subnormal free testosterone levels were found to be almost 3 times as likely to have diabetes (OR, 2.7; 95% CI, 1.8-4.1). This association remained relatively constant after adjusting for body mass index (BMI) >25 kg/m² (OR, 2.6; 95% CI, 1.7-3.9).

A study of more than 350 men by Kapoor and colleagues took this association a step further, evaluating biochemical measures of testosterone and symptoms of hypogonadism as they relate to the presence of type 2 diabetes.24 Results showed that symptomatic hypogonadism is highly prevalent in men with type 2 diabetes. Erectile dysfunction was the most common symptom of hypogonadism in men with diabetes (70%). Although vascular and neurologic diseases are the most common cause of ED, low testosterone levels may be causative as well.

Metabolic syndrome is associated with subsequent development of type 2 diabetes and cardiovascular disease. Similar to the association between the prevalence of type 2 diabetes and low levels of testosterone, it has been found that low testosterone levels are associated with a higher prevalence of metabolic syndrome.25

One study showed that lower levels of testosterone and SHBG in aging men are independently associated with a lower insulin sensitivity and an increased risk of metabolic syndrome.25 An interesting finding of this study was that low testosterone may be a better predictor of metabolic syndrome in thinner men (BMI <25 kg/m²) than in men with higher BMI. Kupelian and colleagues showed that low serum SHBG, total testosterone, and androgen deficiency are associated with an increased risk of developing metabolic syndrome.26

Although the physiologic reason has not been established, it has been shown that, as BMI increases, there is a parallel decrease in total and free testosterone levels.27 Not surprisingly, in another study that looked at the effect of weight loss on testosterone levels in 58 obese men with metabolic syndrome, after 10 weeks, men who had lost a large amount of weight also had an increase in testosterone.24 At week 50, even though some men had regained the weight, 21% were hypogonadal, compared with 48% at baseline.

Another condition seen often in primary care is depression. The Rancho Bernardo Study showed an association between bioavailable testosterone and depression (N=856; men aged 50-89 years), as measured by Beck Depression Index scores.29 These results and others suggest that testosterone therapy may improve depressed mood in older men with low levels of bioavailable testosterone.29,30

There are data that suggest that men with prostate cancer who are receiving gonadotropin-releasing hormone therapy are at greater risk for diabetes and coronary artery disease.31 More than 73,000 Medicare-insured patients 66 years of age or older with prostate cancer were evaluated for a median of 4.5 years after prostatectomy. Androgen deprivation treatment resulted in a significant increase in risk for diabetes (hazard ratio [HR], 1.44; 95% CI, 1.34-1.55) and coronary heart disease (HR, 1.16; 95% CI, 1.20-1.21; \( P < .001 \) for both). Discussion about the potential adverse effects of androgen deprivation with prostate cancer patients appears appropriate.

In many cases, primary care clinicians can successfully treat men with hypogonadism, but there are some instances when a team approach would be more appropriate. A primary care clinician should consider referring a patient to an endocrinologist if he

---

**Table 3. Clinical Manifestations of Hypogonadism**

<table>
<thead>
<tr>
<th>Physical/Metabolic</th>
<th>Psychological</th>
<th>Sexual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased bone mineral density</td>
<td>Decreased mood, diminished energy, sense of vitality, or well-being</td>
<td>Diminished libido, erectile dysfunction, difficulty achieving orgasm, decreased spontaneous erections</td>
</tr>
<tr>
<td>Decreased muscle mass and strength</td>
<td>Impaired cognition and memory</td>
<td></td>
</tr>
<tr>
<td>Gynecomastia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frailty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased body fat or BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin resistance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BMI, body mass index.
exhibits any signs or symptoms of a pituitary tumor, including visual field abnormalities, headaches, hyperprolactinemia, or hypopituitarism. A patient should be referred to a urologist if he has a prostate-specific antigen (PSA) level >4.0 ng/mL, a yearly increase of 1.5 ng/mL or a yearly increase in PSA of >0.75 ng/mL over a 2-year period, a prostate abnormality detected by digital rectal examination (DRE), or an American Urological Association score or International Prostate Symptom Score >19. Other specialists who may become involved in the treatment of patients with low testosterone levels are cardiologists and sleep specialists.

Clinicians need to be aware of androgen deficiency and its causes, effects, and associations with myriad health conditions. The relationships between testosterone and coronary artery disease, diabetes, metabolic syndrome, obesity, and BMI are significant. Because primary care clinicians are on the frontline of recognizing, diagnosing, and treating hypogonadism, it is important for them to be aware of the nuances and challenges associated with this disorder, as well as its potential value as a predictor of future disease risk. Many treatment options are available to the primary care clinician; however, for the complex case, a team approach may be warranted.
Aging Male Symptoms (AMS) rating scale, and the MMAS questionnaire. However, the sensitivity, specificity, and predictive value of these tools have not yet been established in large population-based surveys, and their clinical use is not encouraged.

Finally, measurement of total serum testosterone levels is important in diagnosing hypogonadism; however, in men with conditions that will markedly alter their SHBG, such as obesity, chronic inflammatory disease (eg, as seen with HIV), hyperthyroidism, and liver disease, and in older men who have higher SHBG with borderline free testosterone (200-350 ng/dL), free testosterone should be measured as a helpful adjunct. Free testosterone should be measured with either the mass action equation or equilibrium dialysis in an experienced laboratory. Figure 3 illustrates a workup algorithm for patients with hypogonadism.

HYPOGONADISM TREATMENT CONSIDERATIONS, MONITORING, AND FOLLOW-UP

Adrian S. Dobs, MD, MHS

When treating patients with male hypogonadism, it is important to have specific goals and parameters for monitoring safety and efficacy. Also, to help ensure treatment adherence and thereby maximize treatment outcomes, patient education and counseling are an important part of the treatment plan and should occur in combination with follow-up evaluations.

According to available data, a common treatment target for the average man is a total testosterone level of 500 ng/dL, with a slight decrease to 400 ng/dL in elderly men or those with a history of prostate cancer, although this is an area of much debate. It is clear from total mortality studies that levels of total testosterone should be no less than 250 ng/dL. Clinicians should be aware that the timing of measurements should be based on the pharmacokinetics of the testosterone formulations being used. For instance, with gels, measurements should be taken at a consistent time, preferably in the morning prior to the next application. An intermediate-acting injectable would best be monitored at a mid-interval measurement, whereas midcycle and trough values would be considered with a long-acting injectable.

When monitoring testosterone therapy, it is equally important to assess the efficacy of treatment with regard to the signs and symptoms of low testosterone, particularly psychosocial aspects. Loss of libido and ED are hallmark symptoms of hypogonadism. Lethargy, or loss of energy, is also commonly seen in these men. Furthermore, reduced muscle mass, muscle strength, and increased fat mass are associated with low testosterone levels. Because hypogonadism is characterized by testicular dysfunction, production of sperm is often impaired, resulting in oligospermia or even azoospermia. A deficiency of endogenous testosterone has a deleterious effect on bone mass and is a risk factor for osteoporosis. Regression of secondary sexual characteristics, such as reduced ancillary and pubic hair, is another sign of hypogonadism in men. Mood and behavioral symptoms, namely depression and irritability, may also occur with low testosterone levels.

Treatment of low testosterone with testosterone therapy may provide patients with significant improvements in a variety of areas. In one placebo-controlled study, administration of testosterone therapy resulted in increased BMD and lean body mass, a decrease in fat mass, improved sexual desire, and improved sexual performance. This 12-month study of 371 hypogonadal men demonstrated that testosterone therapy resulted in a significant increase in lean body mass (1.7 kg at month 6; 2.2 kg at month 12; P<.001) and significant decrease in fat mass (1.2 kg at month 6; 1.8 kg at month 12) from baseline; there was no significant change in total body mass. Sexual function, as measured by sexual desire, performance, motivation, satisfaction with erection duration, percentage of full erection, and spontaneous erections, showed significant improvement from baseline at all visits of the extension study (P<.001). The magnitude of effect may vary, however, based on the presence of comorbidities, such as diabetes or atherosclerosis, which have direct effects on erectile function. Improvements in mood were observed and were maintained over the course of the study. There was also a significant (P<.001) change in BMD of the lumbar spine, as measured by dual-energy x-ray absorptiometry (DEXA). When monitoring treatment efficacy, the improvement in BMD may be used to illustrate end-organ benefit to patients who may not see improvement in their sexual parameters.

Although testosterone therapy is known to increase BMD in healthy, hypogonadal men, its effects on fracture risk in older hypogonadal men, who are at increased risk for fractures, have not been evaluated. A 36-month, randomized, double-blind, placebo-controlled trial analyzed 70 men aged 65 years and older with a serum testosterone level less than 350 ng/dL to determine the effects on BMD of intramuscular testosterone enanthate (200 mg every 2 weeks) with or without oral finasteride (5 mg/day). Fifty men completed the 36-month study; all were included (for as long as they contributed data) in an intent-to-treat analysis. Testosterone treatment with or without finasteride significantly increased lumbar BMD from baseline (P<.001) at all time measurements. Increases in lumbar BMD correlated positively with the magnitude of increase in serum total testosterone (r=0.44, P=.001).
Further evidence is found in a meta-analysis performed by Trac and colleagues, which showed a consistent improvement in BMD values with testosterone therapy. Large, long-term randomized trials to evaluate testosterone treatment effect on fracture in patients with and without a history of osteoporotic fracture are needed.

Another area of interest is the beneficial effect of testosterone therapy on metabolic syndrome and its components. Kapoor and colleagues looked at the effect of exogenous testosterone on insulin resistance and glycemic control, visceral adiposity, and dyslipidemia in 24 hypogonadal men who were older than 30 years and had type 2 diabetes. They found that testosterone therapy improved fasting insulin sensitivity, as measured by the homeostasis model assessment index (-1.73, P=.02), which is a ratio of insulin levels and fasting glucose levels. Glycosylated hemoglobin and fasting blood glucose were reduced (-0.37 and -1.58 mmol/L, respectively; P=.03 for both). Visceral adiposity, as measured by waist circumference, was reduced (-1.63 cm, P=.03), as was waist:hip ratio (-0.30, P=.01). There was also a decrease in total cholesterol (-0.4 mmol/L, P=.03); however, no effect on blood pressure was observed. Confirmation of these findings and larger studies are needed.

With regard to monitoring for efficacy of testosterone therapy, it is important to assess and monitor symptoms, obtain a DEXA scan every 2 to 5 years, address glucose and lipid issues, and reinforce the benefits of a healthy lifestyle.

Several potential adverse effects associated with all testosterone therapies are acne, edema in patients with pre-existing conditions, gynecomastia, erythrocytosis, possible sleep apnea, testicular atrophy, and suppression of the hypothalamic-pituitary-gonadal axis. Although there have been case reports of breast cancer developing in men receiving testosterone, it is generally not believed to be a risk.

Testosterone therapy may be associated with increases in hematocrit. Although some increase in hematocrit can be positive, Tenover conducted a study of the effects of testosterone supplementation in 13 healthy older men (age range, 57-76 years; mean age, 67.5 years) with serum testosterone levels ≤13.9 nmol/L (400 ng/dL). Testosterone enanthate (100 mg/week intramuscularly for 3 months) produced a highly significant increase (P<.001) in mean hematocrit from baseline (from 43.1% to 46.7%), mean erythrocyte count (from 4.74 x 10⁶/µL to 5.20 x 10⁶/µL), and mean hemoglobin (from 14.7 to 15.5 g/dL). Testosterone therapy also produced significant decreases (P<.05) in mean total cholesterol and low-density lipoprotein (LDL; from 199 to 177 mg/dL and from 128 to 113 mg/dL, respectively).

A meta-analysis of randomized, placebo-controlled trials by Calof and colleagues revealed that testosterone therapy in older men was associated with a significantly higher risk of hematocrit being >50%, confirming the need to carefully monitor hematocrit levels in this population. Of note, it has not been shown that elevated hematocrit increases the risk of cardiovascular disease (OR, 1.16; CI, 1.05-1.29) and testosterone does not worsen—and may in fact improve—coronary artery disease. Further, this study demonstrated that low-dose testosterone therapy improved angina threshold and exercise-induced myocardial ischemia.

A study of 29 hypogonadal men treated with transdermal testosterone found that the changes in serum lipoproteins appear consistent with those of the physiologic effects of testosterone in eugonadal men. With regard to high-density lipoprotein (HDL), men with the highest testosterone levels have the healthiest HDL levels, most likely because men with low testosterone tend to be obese and, therefore, have worse HDL levels.

As with any therapy, it is important to monitor patients receiving testosterone therapy. A symptom assessment should be performed at 1 to 2 months after initiating therapy, again at 3 to 6 months, and annually thereafter. Any occurrence of adverse events should be noted. Testosterone levels should be measured in the beginning and then annually to ensure goals are being met. A breast examination should be performed at 6 months and annually, with mammograms taken as indicated, and hematocrit should be measured at 3 months and annually. If hematocrit is 54%, then the testosterone dose should be reduced (Table 4).

After clinicians identify hypogonadism and begin treatment, it is important, along with monitoring for safety and efficacy, to counsel patients. Appropriate counseling and education—explaining that testosterone therapy should not be solely equated with sexual function; setting realistic expectations; and describing the risks, benefits, and perceived fears of therapy—will help to increase adherence and improve patient outcomes.

### Table 4. Monitoring During Testosterone Therapy

<table>
<thead>
<tr>
<th>Monitoring</th>
<th>1-2 mo</th>
<th>3-6 mo</th>
<th>Annually</th>
<th>Goals/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Evaluate whether symptoms have responded to treatment and whether there are adverse effects</td>
</tr>
<tr>
<td>Testosterone level</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Provide therapy to raise serum testosterone levels into the mid-normal range</td>
</tr>
<tr>
<td>Breast examination</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Order mammograms only as indicated</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>If hematocrit is &gt;54%, stop therapy until hematocrit decreases to a safe level</td>
</tr>
<tr>
<td>IPSS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Obtain urological consultation if IPSS score is &gt;19</td>
</tr>
<tr>
<td>PSA</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Biopsy if PSA is ≥4.0 ng/mL. Biopsy if PSA increases by 2.1 ng/mL within any 12-mo period. Repeat PSA measurement for PSA increase of 0.7-10.0 ng/mL in 1 y</td>
</tr>
<tr>
<td>DRE</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Biopsy if abnormal baseline and if abnormal during treatment</td>
</tr>
<tr>
<td>DEXA</td>
<td></td>
<td></td>
<td>X</td>
<td>Measure bone mineral density of lumbar spine and/or femoral neck after ≥1-y of treatment in hypogonadal men with osteoporosis or low trauma fracture</td>
</tr>
</tbody>
</table>

DEXA, dual-energy x-ray absorptiometry; DRE, digital rectal examination; IPSS, international prostate symptom score; PSA, prostate-specific antigens.
NOVEL TESTOSTERONE FORMULATIONS AND DOSING: POTENTIAL IMPACT ON TREATMENT AND OUTCOMES

Ajay Nehra, MD

Since the introduction of subdermal implants of testosterone in the 1940s, there have been many improvements in testosterone treatment options. Accordingly, there has been an increase in the use of testosterone therapy. In 2004, it was estimated that 2.4 million prescriptions were written for testosterone in the United States, more than double the number written in 2000. A variety of testosterone formulations are available in the marketplace today, differentiated by cost, delivery route, and effectiveness in providing physiologic levels of testosterone, as well as delivery system-specific side effects.

Since the introduction of gel formulations in 2000, the steady annual increase in the use of this type of product supersedes the percent increase in the overall use of testosterone. It has been estimated that more than 65% of testosterone prescriptions are written for gels, 17% for injectables, almost 12% for patches, and 3% for orals, with the remainder for buccals or other formulations. With the variety of preparations available, it seems that most clinicians settle for gel preparations over intermediate-term injectables.

An ideal testosterone therapy should be safe, cost-effective, and convenient for the patient while achieving and maintaining constant, clinically therapeutic testosterone levels. Table 5 provides an overview of the current and novel testosterone formulations, their dosages, and potential formulation-specific adverse effects. Table 6 summarizes the pros and cons of the testosterone formulations.

In the United States, product labels for testosterone formulations contain warnings regarding prostatic hyperplasia, suppression of spermatogenesis, acne and oily skin, gynecomastia, and fluid retention. The labeling for the buccal system also includes a warning that the treatment of hypogonadal men with testosterone esters may potentiate sleep apnea, especially in patients with risk factors such as obesity or chronic lung disease. The Endocrine Society clinical practice guidelines for testosterone therapy state that sleep apnea is infrequent in young hypogonadal men. As noted by the American Association of Clinical Endocrinologists guidelines, despite anecdotal reports, no causal relationship has been established between testosterone treatment and prostate cancer.

A novel intramuscular injection formulation administered 5 times a year, testosterone undecanoate, is being evaluated for use in the United States. It was approved and launched in Europe and Asia in a dosage of 1000 mg in 4 mL of castor oil administered up to every 12 weeks. The anticipated dose in the United States will be 750 mg in 3 mL of castor oil administered every 10 weeks following a 4-week loading interval. Testosterone undecanoate maintains eugonadal levels of testosterone even when injection intervals are increased from 6 to 12 weeks. In an open-label, nonrandomized study, 7 men aged 20 to 57 years with hypogonadism who had participated in a previous trial of 6-week injections agreed to continue treatment. The men received 4 injections at 6-week intervals, and then the intervals were increased between the 5th and 10th weeks. From the 10th week onward, testosterone undecanoate was injected every 12 weeks. Weekly measurement of testosterone demonstrated steady-state kinetics after the 13th injection.

An open-label, randomized, prospective trial evaluated the pharmacokinetics of testosterone enanthate and testosterone undecanoate administered to 40 hypogonadal men (20 men per

Table 5. Dosages and Adverse Effects of Testosterone Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dosage</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injectable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pellet implants**</td>
<td>Four 500-mg subcutaneous pellets every 5-7 mo</td>
<td>Potential infections or expulsion</td>
</tr>
<tr>
<td>Testosterone cypionate and testesterone enanthate</td>
<td>50-400 mg every 1-4 wk</td>
<td>Mood fluctuations or changes in rhythm; pain at injection site; excessive erythrocyclodes</td>
</tr>
<tr>
<td>Testosterone undecanoate**</td>
<td>1000 mg every 8 wk during first 12 wk, then 1000 mg every 3 mo</td>
<td>Pain at injection site</td>
</tr>
<tr>
<td><strong>Topical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical gel**</td>
<td>5-10 g daily</td>
<td>Dermal testosterone transference</td>
</tr>
<tr>
<td>Transdermal patch system**</td>
<td>5 mg daily</td>
<td>Skin irritation</td>
</tr>
<tr>
<td><strong>Oral</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buccal system**</td>
<td>30 mg every 12 h</td>
<td>Alterations in taste and irritation of gums and oral mucosa</td>
</tr>
<tr>
<td>Fluymesterone**</td>
<td>30 mg every 12 h</td>
<td>Alterations in taste and irritation of gums and oral mucosa</td>
</tr>
<tr>
<td>Testosterone undecanoate**</td>
<td>120-180 mg daily divided into 2 or 3 doses</td>
<td>Low serum testosterone levels during part of the day</td>
</tr>
</tbody>
</table>

*46,49,51,53-55 The labeling for the buccal system also includes a warning that the treatment of hypogonadal men with testosterone esters may potentiate sleep apnea, especially in patients with risk factors such as obesity or chronic lung disease. The Endocrine Society clinical practice guidelines for testosterone therapy state that sleep apnea is infrequent in young hypogonadal men. As noted by the American Association of Clinical Endocrinologists guidelines, despite anecdotal reports, no causal relationship has been established between testosterone treatment and prostate cancer.*

Table 6. Advantages and Disadvantages of Available Testosterone Formulations

<table>
<thead>
<tr>
<th>Type</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injectable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transdermal patch</td>
<td>Testosterone levels mimic circadian rhythm</td>
<td>Moderate cost</td>
</tr>
<tr>
<td></td>
<td>Low incidence of polyuria</td>
<td>Visible, not discreet</td>
</tr>
<tr>
<td>Buccal system**</td>
<td>Maintain testosterone concentration over 24-h period</td>
<td>High patient adherence</td>
</tr>
<tr>
<td>Testosterone undecanoate**</td>
<td>Expensive</td>
<td>Concerns regarding transference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug accumulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Variable absorption</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Messy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily administration</td>
</tr>
<tr>
<td><strong>Topical</strong></td>
<td>Irritants</td>
<td></td>
</tr>
<tr>
<td>Topical gel**</td>
<td>Effective in relieving symptoms</td>
<td>Supraphysiologic fluctuations</td>
</tr>
<tr>
<td><strong>Oral</strong></td>
<td></td>
<td>Can be painful</td>
</tr>
<tr>
<td>Buccal</td>
<td></td>
<td>Requires office visit every 2 wk</td>
</tr>
</tbody>
</table>
treatment) as long-term treatment for male hypogonadism. Testosterone enanthate was administered intramuscularly in a dosage of 250 mg every 3 weeks, and testosterone undecanoate was administered in a dosage of 1000 mg every 6 weeks (loading dose) followed by one 1000-mg dose after an additional 9 weeks (Figure 4). Serum testosterone concentrations in the 2 treatment groups were comparable at baseline and well below the normal adult range of 10 to 30 nmol/L, with values of 2.67±2.31 nmol/L in the testosterone enanthate group and 3.94±4.35 nmol/L in the testosterone undecanoate group. Men receiving testosterone undecanoate had significantly higher trough levels of serum testosterone after 12 and 30 weeks of therapy than men receiving testosterone enanthate. Values in the testosterone undecanoate and testosterone enanthate groups were 14.14±4.48 nmol/L and 8.02±3.66 nmol/L (P<.0001), respectively. After 30 weeks, values were 16.31±5.66 nmol/L in the testosterone undecanoate group and 8.29±3.99 nmol/L in the testosterone enanthate group (P<.0001). Slow accumulation of serum testosterone was detected at the end of the 6-week dosing intervals in men receiving testosterone undecanoate, but this was prevented by increasing the dosing interval to 9 weeks.

These findings indicate that testosterone undecanoate 1000 mg injected at 12-week intervals was well tolerated and maintained sustained therapeutic levels of testosterone throughout the dosing interval when administered every 6 to 9 weeks. Over the 2-year treatment period, there were no local adverse effects at the site of injection and no complaints by patients about pain or discomfort. Further, when given the option to switch back to a testosterone enanthate preparation, all of the patients chose to continue taking the testosterone undecanoate formulation, and all agreed to participate in an extension of the study period.

Saad and colleagues evaluated the long-term use of testosterone undecanoate in men receiving therapy for up to 8.5 years. Twenty-two hypogonadal men aged 30 to 65 years (mean age, 43.8 years) received injections of testosterone undecanoate 1000 mg for up to 8.5 years. Sexual function was restored, and positive mood changes were reported. Hematocrit and hemoglobin concentrations were elevated; however, they remained within normal ranges. Prostate size was measured by transrectal ultrasound, and all were <30 mL. PSA concentrations did not exceed 2.0 ng/mL. In general, bone density, as measured by quantitative computed tomography of the lumbar spine or phalangeal ultrasonography, improved and plateaued after 2 years of treatment. Changes in other metabolic parameters generally occurred within the first 6 months of therapy. The only adverse effect was moderate local irritation at the injection site, which did not last longer than 3 days.

When symptoms of metabolic syndrome were evaluated, it was shown that testosterone undecanoate conferred a more beneficial effect than did testosterone gel, indicating a relationship between plasma testosterone and effect on metabolic syndrome. Significant decreases (P<.05) were seen in waist circumference, total cholesterol, LDL, and triglycerides, and an increase was seen in HDL with testosterone undecanoate versus testosterone gel. Also significantly improved were the AMS score and the International Index of Erectile Function scores with testosterone undecanoate versus testosterone gel (P<.05 for each). There were slight reductions in blood pressure. There were no changes in glucose, liver function, PSA levels, or hemoglobin and hematocrit concentrations and no significant side effects. As some benefits may take at least a year to manifest, it is possible that testosterone undecanoate may have further positive effects not illustrated by this 9-month study.

As with any pharmacotherapy, adherence to treatment is important for positive outcomes, and side effects can compromise adherence. Cutaneous side effects are common with transdermal patches, the most common being irritation and contact dermatitis. In one open-label crossover study of the testosterone patch, 12% of patients using a nonscrotal transdermal system had allergic skin reactions. The 12-week administration schedule of testosterone undecanoate may eliminate adherence issues and thereby improve patient outcomes and quality of life.

Overall, the long-acting testosterone undecanoate formulation offers many benefits, including efficacy, safety, and a more convenient dosing interval, and may prove to be a valuable addition to the armamentarium of testosterone therapies. More experience with testosterone undecanoate is needed in older men who are at higher risk for developing erythrocytosis and prostate-related complications.
It is well established that prostate growth, both normal and abnormal, depends to some degree on the presence of androgens. The Prostate Cancer Prevention Trial (PCPT) is the largest and longest prevention trial in urology (N=18,882).66 The investigators demonstrated that, when DHT is reduced with the administration of finasteride, the period prevalence of prostate cancer is lowered by 25% over 7 years (P<.001). The conclusion drawn from this study is that use of a 5α-reductase inhibitor can prevent or delay the development of prostate cancer; however, this benefit comes with a small increased risk of sexual side effects and possibly high-grade prostate cancer.

The effects and risks of testosterone therapy on prostate health have not yet been fully elucidated, and there is pervasive concern about prostate safety when aging men receive supplemental testosterone. A belief has persisted for generations that negative outcomes are associated with the exposure of the prostate to increased levels of testosterone.

Evidence that endogenous testosterone stimulates the prostate has come from various sources with conflicting results. In testosterone therapy clinical trials involving hypogonadal men, there is no increase in prostate cancer with testosterone compared with placebo to support this theory; however, these trials were not powered to assess this issue. Animal models of prostate cancer have shown testosterone to be a weak carcinogen, and a recent meta-analysis evaluating the relationship of endogenous testosterone to future development of prostate cancer concluded that endogenous testosterone had no influence on prostate cancer.67 However, in men with advanced prostate cancer, there is convincing evidence that testosterone is harmful and contraindicated.

A report published in Urology showed that, in 33 men with painful bony metastases who were treated with phosphorus-32 therapy (androgen priming, parathormone rebound, or combination therapy), all patients reported intensified pain with testosterone, and 2 patients experienced paraplegia.68

To determine the effects of testosterone therapy on the tissue of the prostate gland of men with late-onset hypogonadism, a randomized, double-blind, placebo-controlled trial was conducted in a US community-based research center (N=44).9 It was hypothesized that exogenous testosterone would increase testosterone and DHT in the prostate and cause biologic changes in the gland. The primary outcome measure was the change in levels of testosterone and DHT in the prostate after 6 months. Men aged 44 to 78 years with a testosterone level <300 ng/dL and symptoms related to late-onset hypogonadism were eligible for this study. After screening 107 volunteers, 48 patients were enrolled in the study (19 did not meet eligibility requirements, and 40 declined to participate). In 4 patients, cancer of the prostate was detected upon biopsy, resulting in 44 patients who were randomized to receive either testosterone 150 mg (n=22) or placebo (n=22) intramuscularly every 2 weeks for 6 months. More than 99% of patients adhered to the prescribed dosing regimen. Groups were relatively well matched for age, race, BMI, testosterone levels, prostatic measure of volume, PSA levels (higher in the testosterone group than in placebo), voiding symptoms, and urinary flow rate. In the testosterone therapy group, 1 patient discontinued because of erythrocystosis, and 3 in the placebo group were excluded from analysis (1 moved, gastrointestinal cancer developed in 1, and 1 had normal baseline testosterone level). Biopsy cores of tissue (wet weight, 5-10 mg) from the prostate gland were analyzed chemically, histologically, and genetically.

Results showed that, although serum levels of testosterone and DHT rose as expected, there were no corresponding increases in tissue testosterone or DHT (Figure 5).9 Regarding secondary outcome measures, there were no increases in histologic parameters of atrophy, inflammation, or prostatic intraepithelial neoplasia. The stroma:epithelial ratio remained stable, as did other important biomarkers (eg, Ki-67 for cell proliferation, androgen receptor, CD34 for angiogenesis) and mRNA expression for PSA, vascular endothelial growth factor (VEGF-A), and clusterin. This stability with regard to gene expression indicates that the testosterone therapy was not changing the biology of the prostate gland. During the trial, a total of 10 cancers were detected, 6 of which were detected at exit biopsy. Four of these cases were found in the placebo group (n=19) and 2 in the testosterone group (n=21), most of which were small and well differentiated. The investigators concluded that the risks to the prostate from testosterone therapy (of 6 months’ duration) may not be as great as once feared. However, they cautioned that these data do not ensure prostate safety for large populations of older men who...
may have highly prevalent subclinical disease or who may undergo a longer duration of therapy.

These data add an element of prostate safety to testosterone therapy that has been missing. From a physiologic perspective, these results suggest that the prostate, in effect, buffers itself against an influx of testosterone. Additional research is needed regarding the safety of testosterone therapy in older men; however, the risks to the prostate may not be as great as supposed in the historically held belief.

**TESTOSTERONE AND THE PROSTATE: WHAT IS THE RELATIONSHIP?**

Abraham Morgentaler, MD

There is a belief widely held by the medical community, particularly urologists, that low testosterone levels protect against prostate cancer and that, conversely, elevated testosterone is a risk factor for cancer growth. Testosterone has been likened to “food for a hungry tumor.” This belief is historical, but simplistic and contrary to a large body of evidence. It is perhaps the single greatest hurdle to initiating testosterone therapy.

The research that begat the belief that testosterone increases the growth of prostate cancer was published by Huggins and Hodges in 1941 in *Cancer Research*. These investigators concluded that reducing testosterone to castrate levels causes the regression of prostate cancer and that increasing testosterone causes “enhanced growth” of prostate cancer.69 The latter conclusion was based on only 2 men, 1 of whom had already been castrated. Thus, the origin of the belief that raising serum testosterone might make prostate cancer grow in an otherwise healthy, untreated individual was based on a single man with widely metastatic disease. In addition, the conclusion was based on serum acid phosphatase levels, the use of which was abandoned with the introduction of PSA testing because of erratic results.

Another published reference that seemingly supported the notion that increased levels of testosterone were associated with prostate cancer outcomes was a review of men with bone metastases at Memorial Sloan-Kettering Cancer Center between 1949 and 1967, which concluded that 45 of 52 men had an “unfavorable response.”70 This “unfavorable response” was poorly defined and included a number of objective and subjective outcomes, such as a rise in acid phosphatase, increased bone pain, or urinary retention. However, of these 52 men, only 4 were hormonally intact; the rest had already been castrated or treated with estrogen. When these 4 men were looked at as a subgroup, only 1 had an unspecified unfavorable response within 30 days; the other 3 men received daily testosterone injections for 52, 55, and 310 days, respectively. The authors concluded that “normal endogenous testosterone levels may be sufficient to cause near-maximal stimulation of prostatic tumors.”

An additional concern is testosterone flare, which refers to a surge in testosterone levels followed by a sharp decrease to castration levels. It occurs 10 to 14 days after a luteinizing hormone-releasing hormone (LHRH) agonist is administered. Testosterone flare has been associated with such negative outcomes as vertebral collapse, urinary retention, and worsening bone pain. However, only 2 papers in the literature looked at PSA during this flare, and neither showed a rise in PSA levels.71,72

One of these studies was an open-label phase 2 trial that involved 242 men with prostate cancer who required initial hormonal treatment and received abarelix depot (n=209) or LHRH agonists (n=33) with or without antiandrogen.72 Results showed that testosterone levels rose by about 50%, from almost 500 ng/dL to more than 700 ng/dL, in 4 days and then rapidly declined. During the period of flare, PSA levels remained constant and then dropped dramatically when testosterone declined (Figure 6).

Although there is no question that prostate cancer is androgen-dependent with regression of metastatic disease upon medical or surgical castration, this does not necessarily mean that higher testosterone leads to greater prostate cancer growth. The available evidence strongly indicates that the relationship between testosterone and prostate cancer is more complex. Changes in testosterone within the near-castrate range produce significant changes in prostate cancer growth, whereas changes in testosterone above this range do not appear to impact prostate cancer growth (Figure 7). This suggests a saturation curve. In other words, there is a limit to the ability of testosterone to stimulate additional prostate cancer growth.

Paradoxically, there is the issue of low testosterone levels being associated with several negative aspects of prostate cancer, including higher Gleason scores, more advanced age at presentation, and more negative outcomes. One study of 345 hypogonadal men with PSA levels of 4.0 ng/mL or less showed an increased risk of prostate cancer associated with lower levels of testosterone.74 Cancer occurred in 21% of men with testosterone levels ≤250 ng/dL compared with 12% of men with levels >250 ng/dL (P=.04). Similarly, cancer was detected in 20% of men with free
testosterone levels of ≤1.0 ng/dL compared with 12% of men with levels >1.0 ng/dL (P=.04).

A paradox also exists when one looks at the percentage of men with prostate cancer in the general population compared with that in testosterone therapy trials. About 15% of men with PSA levels <4.0 ng/mL have biopsy-detectable prostate cancer, whereas there is only a 1% detection rate in testosterone therapy trials. If raising testosterone levels were to increase the risk of prostate cancer, one would expect that, in trials of men receiving testosterone, there would be a higher percentage of prostate cancer. The same is true for the age-related incidence of prostate cancer, which begins as men enter their 40s, not their 20s, the peak of testosterone production. In fact, the prevalence of prostate cancer increases inversely as testosterone levels decline with age.

The historical concept that an increase in testosterone will cause an increase in prostate cancer is overly simplistic and contrary to a large body of evidence, which instead supports a saturation curve or threshold beyond which increasing testosterone has no effect. Instead of calling testosterone “food for a hungry tumor,” a more appropriate analogy compares testosterone to “water for a thirsty tumor,” and once the thirst has been satisfied, more water will have no further effect. A more relevant and important concern is the emerging recognition of a worrisome relationship between low testosterone levels and prostate cancer, which requires further investigation.

**Figure 7. Relationship Between Testosterone and Prostate Cancer**

![Graph showing relationship between testosterone and prostate cancer growth](image)

The relationship between testosterone and the prostate is an area of concern and controversy, especially with regard to men who have been treated for prostate cancer. How does testosterone therapy affect the relationship between low testosterone and treated prostate disease? How does the conundrum regarding testosterone therapy affect how clinicians approach monitoring and treating patients after they have undergone prostatectomy or brachytherapy? In truth, data are lacking, with only 2 published reports involving 17 patients with a median follow-up of 2 years after radical prostatectomy75-76 and 1 study of testosterone therapy after brachytherapy.77 Further, there are unanswered questions regarding the correlation of benign prostatic hyperplasia (BPH) risk with testosterone treatment. This is of particular importance for hypogonadal older men, who may already be at risk for BPH.

DHT is the androgen primarily responsible for the growth and enlargement of the prostate. It has been established through epidemiologic studies that levels of testosterone decrease exponentially as men age, whereas levels of DHT remain relatively constant. Preventing the conversion of testosterone to DHT could result in a decreased androgen effect that, in the prostate, could decrease BPH and its associated symptoms of urinary obstruction. This was evident in a double-blind study to evaluate the safety and efficacy of finasteride, a 5α-reductase inhibitor, in men with BPH.78 It was found that finasteride had a significant effect on prostate size and indirectly alleviated the lower urinary tract symptoms (LUTS) often associated with BPH.

It has also been shown that testosterone therapy did not raise the level of DHT significantly and did not result in a significant increase in incidence of BPH in hypogonadal men compared with eugonadal men. What is known about testosterone and LUTS? Approximately 20% of older men with LUTS are hypogonadal. One study has shown that elderly hypogonadal patients receiving intramuscular testosterone therapy experienced fewer bladder outlet obstruction symptoms than younger hypogonadal men receiving intramuscular testosterone.79 More studies are needed to investigate the effect of testosterone therapy on the development of BPH. With no evidence that testosterone therapy accelerates BPH, hypogonadal patients may be treated with testosterone with careful monitoring.79

Regarding testosterone therapy and possible changes in the prostate, several questions are often asked. Does testosterone increase PSA levels? In some men, PSA levels will increase slightly, but not significantly.79,80 Does testosterone increase prostate volume? Men receiving testosterone therapy exhibited an increase in prostate size that was comparable with, but not higher than, those in age-matched eugonadal men.81 Does testosterone stimulate the growth of previously undetected tumors? This has not been proved or disproved. What is known is that there are no data to support the concept that testosterone therapy causes new prostate cancer.80,82

A retrospective study of PSA variability and velocity was undertaken to determine the most appropriate sampling interval and PSA velocity (the deviation in PSA between measurements relative to the elapsed time between measurements) to help identify men with prostate cancer.83 Patients were part of the Baltimore Longitudinal Study of Aging and were divided into 3 groups: men

**MONITORING AND TREATMENT AFTER PROSTATECTOMY OR BRACHYTERAPY**

E. David Crawford, MD

The relationship between testosterone and the prostate is an area of concern and controversy, especially with regard to men who have been treated for prostate cancer. How does testosterone therapy affect the relationship between low testosterone and treated prostate disease? How does the conundrum regarding testosterone therapy affect how clinicians approach monitoring and treating patients after they have undergone prostatectomy or brachytherapy? In truth, data are lacking, with only 2 published reports involving 17 patients with a median follow-up of 2 years after radical prostatectomy75-76 and 1 study of testosterone therapy after brachytherapy.77 Further, there are unanswered questions regarding the correlation of benign prostatic hyperplasia (BPH) risk with testosterone treatment. This is of particular importance for hypogonadal older men, who may already be at risk for BPH.

DHT is the androgen primarily responsible for the growth and enlargement of the prostate. It has been established through epidemiologic studies that levels of testosterone decrease exponentially as men age, whereas levels of DHT remain relatively constant. Preventing the conversion of testosterone to DHT could result in a decreased androgen effect that, in the prostate, could decrease BPH and its associated symptoms of urinary obstruction. This was evident in a double-blind study to evaluate the safety and efficacy of finasteride, a 5α-reductase inhibitor, in men with BPH.78 It was found that finasteride had a significant effect on prostate size and indirectly alleviated the lower urinary tract symptoms (LUTS) often associated with BPH.

It has also been shown that testosterone therapy did not raise the level of DHT significantly and did not result in a significant increase in incidence of BPH in hypogonadal men compared with eugonadal men. What is known about testosterone and LUTS? Approximately 20% of older men with LUTS are hypogonadal. One study has shown that elderly hypogonadal patients receiving intramuscular testosterone therapy experienced fewer bladder outlet obstruction symptoms than younger hypogonadal men receiving intramuscular testosterone.79 More studies are needed to investigate the effect of testosterone therapy on the development of BPH. With no evidence that testosterone therapy accelerates BPH, hypogonadal patients may be treated with testosterone with careful monitoring.79

Regarding testosterone therapy and possible changes in the prostate, several questions are often asked. Does testosterone increase PSA levels? In some men, PSA levels will increase slightly, but not significantly.79,80 Does testosterone increase prostate volume? Men receiving testosterone therapy exhibited an increase in prostate size that was comparable with, but not higher than, those in age-matched eugonadal men.81 Does testosterone stimulate the growth of previously undetected tumors? This has not been proved or disproved. What is known is that there are no data to support the concept that testosterone therapy causes new prostate cancer.80,82

A retrospective study of PSA variability and velocity was undertaken to determine the most appropriate sampling interval and PSA velocity (the deviation in PSA between measurements relative to the elapsed time between measurements) to help identify men with prostate cancer.83 Patients were part of the Baltimore Longitudinal Study of Aging and were divided into 3 groups: men
Androgen receptor expression was also determined in a subgroup of clinical workup and measurements of total testosterone, LH, follicle-stimulating hormone (FSH), estradiol, and dehydroepiandrosterone. Partial androgen deficiency, defined as serum testosterone <3.0 ng/mL, was found in 33% of the men, who also had lower LH, FSH, and estradiol compared with men whose testosterone levels were ≥3.0 ng/mL. Mean Gleason scores were found to be significantly higher (7.4 vs 6.2, P<.001) and PSA levels were lower (25.3 vs 31.9 ng/mL) in the group with lower testosterone levels. The investigators concluded that patients with low serum testosterone levels present with higher grade cancers and that there is a possible tumor-mediated suppression of the hypothalamic-pituitary-gonadal axis in men with high Gleason scores, as suggested by their lower levels of LH, FSH, and estradiol.

Testosterone therapy increases prostate volume to the same extent as that in age-matched controls. Continued treatment, however, does not increase prostate volume supraphysiologically. Testosterone therapy also restores serum PSA levels to normal in hypogonadal men, and long-term treatment does not raise levels above the normal range. All of this still begs the question regarding the safety of testosterone therapy in men after successful treatment of prostate cancer. As mentioned, published data are very limited. A retrospective review of patients with cancer confined to the prostate who were treated for hypogonadism after radical retropubic prostatectomy was undertaken to determine whether testosterone therapy could be effective and safe without causing recurrent prostate tumor. Ten patients who underwent radical retropubic prostatectomy between 1993 and 2003 were identified. Postoperatively, they had no clinical or PSA evidence of disease but presented with complaints of lower libido, ED, lack of energy, cognitive impairment, hot flushes, or a combination of these symptoms. Baseline serum PSA levels were measured to exclude recurrent prostate cancer, and baseline serum testosterone levels were determined to confirm hypogonadism. The mean age of the men was 64.3 years. Preoperatively, PSA levels were 7.0 ng/mL and testosterone levels (available for 5 patients) were 469 ng/dL. Gleason scores obtained from prostate adenocarcinoma specimens ranged from 6 to 8. Postoperative values for PSA and testosterone were <0.10 ng/mL and 197 ng/dL, respectively. Patients received either topical testosterone gel or patch or intramuscular testosterone cypionate and were followed every 2 months. At follow-up (median, 19 months), there were statistically significant improvements in testosterone levels (197 vs 591 ng/dL, P=.0002) and symptoms of hypogonadism with no detectable increase in PSA levels (>0.1 ng/mL).

Similarly, a retrospective review of clinical records from 2 private urology practices identified 7 hypogonadal men who were treated with testosterone after curative radical prostatectomy and found...

A retrospective analysis by Morgentaler and colleagues published in *JAMA* looked at the prevalence of occult prostate cancer in men with low serum testosterone levels. A total of 77 men (mean age, 58 years) with low total or free testosterone levels who had normal results on DRE and PSA levels <4.0 ng/mL underwent ultrasound-guided sextant prostate needle biopsies. Eleven men were found to have prostate cancer (14%), 10 of whom were 60 years of age or older. This percentage is high in comparison with rates found in screening populations; previously published prevalence rates from several large prostate cancer screening studies in men with normal DRE results and PSA levels <4.0 ng/mL range from 1.8% to 4.5%. When characteristics of men with benign and malignant findings were compared, mean values were found to be relatively similar, including PSA levels (1.2 vs 1.7 ng/mL), prostate volume (35.3 vs 35.0 mL), total testosterone (356.0 vs 419.0 ng/dL), and free testosterone (1.1 vs 1.1 ng/dL). The investigators concluded that DRE and PSA levels are insensitive indicators of prostate cancer in men with low total or free testosterone levels and that PSA levels may be affected by naturally occurring reductions in serum androgen levels. This raises the question about whether testosterone therapy potentially creates a risk in men for whom a decreased androgen status may mask prostate cancer. However, it should be noted that the age at which cancer developed in the men in this analysis was older and that the rate of 14% is similar to that found in the PCPT (n=9000), in which there was a 16% rate of prostate cancer in older men.

Another question relates to whether the level of total testosterone is associated with the grade of prostate cancer at diagnosis. It has been shown that high-grade prostate cancer is associated with a low serum testosterone level (Figure 8). One hundred fifty-six men with a mean age of 66 years were evaluated, including a full clinical workup and measurements of total testosterone, LH, follicle-stimulating hormone (FSH), estradiol, and dehydroepiandrosterone. Androgen receptor expression was also determined in a subgroup of men. Partial androgen deficiency, defined as serum testosterone <3.0 ng/mL, was found in 33% of the men, who also had lower LH, FSH, and estradiol compared with men whose testosterone levels were ≥3.0 ng/mL. Mean Gleason scores were found to be significantly higher (7.4 vs 6.2, P<.001) and PSA levels were lower (25.3 vs 31.9 ng/mL) in the group with lower testosterone levels. The investigators concluded that patients with low serum testosterone levels present with higher grade cancers and that there is a possible tumor-mediated suppression of the hypothalamic-pituitary-gonadal axis in men with high Gleason scores, as suggested by their lower levels of LH, FSH, and estradiol.
no biochemical or clinical evidence of cancer recurrence. Before treatment, all 7 men had clinical symptoms of hypogonadism and low levels of serum testosterone. After follow-up ranging from 1 to 12 years, no evidence of local recurrence or distant spread of prostate cancer was found in the 7 men who received testosterone.

More recently, records of 31 men who underwent prostate brachytherapy between 1996 and 2004 and received subsequent testosterone therapy for hypogonadism were reviewed to assess the risk of biochemical failure or prostate cancer recurrence or progression. The duration of testosterone therapy after prostate brachytherapy ranged from 0.5 to 8.5 years (median, 4.5 years), with a follow-up ranging from 1.5 to 9.0 years (median, 5.0 years). Testosterone therapy was initiated between 0.5 and 4.5 years (median, 2.0 years) after brachytherapy. Median serum testosterone levels were 188 ng/dL before testosterone therapy and rose to 498 ng/dL with testosterone therapy. There was only 1 case of a transient rise in PSA levels, and the most recent measures of PSA showed that 74.2% of patients had levels rise by $<0.1$ ng/mL; 96.7%, $<0.5$ ng/mL; and 100%, $<1.0$ ng/mL. The author concluded, “Given the significant, long-term metabolic derangements and significant symptoms in some hypogonadal patients,” testosterone therapy may be considered for patients who have been treated successfully for early-stage, localized prostate cancer.

Because testosterone affects various organs and tissues, men receiving testosterone therapy should be evaluated at baseline and at follow-up visits, generally at 3 and 6 months after the initiation of therapy and yearly thereafter. If PSA levels increase substantially or an abnormality is detected by DRE, a prostate biopsy should be performed. At follow-up, urinary symptoms and the presence or exacerbation of sleep apnea or gynecomastia should be monitored. Hemoglobin or hematocrit should be monitored during testosterone therapy. The risk of erythrocytosis appears to vary with the type of testosterone formulation.

DRE should be repeated at follow-up visits. If PSA levels are $>4.0$ ng/mL or increase by $\geq 1.0$ ng/mL in a year, a prostate biopsy should be performed or the patient should be referred to a urologist. For increases in PSA levels of 0.7 to 0.9 ng/mL in a year, the PSA measurement should be repeated in 3 to 6 months, and a biopsy should be performed if a further increase is detected.

The use of testosterone therapy for hypogonadism after treatment of prostate cancer is fraught with controversy and concern, conflicting data, and unanswered questions. Overall, available evidence seems to show that hypogonadal men who have been successfully treated for prostate cancer are candidates for testosterone therapy with careful evaluation and monitoring.

CONCLUSION

Hypogonadism is associated with aging and several comorbid conditions: depression, ED, increased BMI and waist circumference, type 2 diabetes, metabolic syndrome, and coronary artery disease. It is important for clinicians to be aware of how testosterone levels can be related to these conditions, which are seen in primary care practices on a daily basis.

Hypogonadism is highly prevalent and may impact mortality, but it is underdiagnosed and undertreated for a variety of reasons. Being aware of these reasons and having a deeper understanding of hypogonadism will help clinicians recognize and treat the disorder. Diagnosing hypogonadism is complicated by various factors, including the lack of a concrete testosterone threshold to define it and the wide variability in assays and laboratory measurements.

A variety of testosterone formulations are available, and the number of prescriptions continues to rise as clinicians (and patients) become more aware of hypogonadism and how to properly diagnosis and treat it. A novel long-acting injectable formulation, testosterone undecanoate, is expected to be approved in the United States in 2008. Testosterone undecanoate offers the advantage of effectively maintaining clinically therapeutic and consistent levels without the adverse effects and inconvenience associated with other formulations. A dosing regimen of every 10 weeks, resulting in 5 injections per year, may improve patient adherence.

Treatment goals should be based on the resolution of signs and symptoms of hypogonadism. Therapy should aim not only to increase the duration of but improve the quality of patients’ lives, to allow them “to reach their full potential regardless of age,” as stated in the American Association of Clinical Endocrinologists guidelines. Treatment with testosterone can provide positive improvements in libido, erectile function, energy, mood, body composition, and BMD. Concerns over the possible negative effects of testosterone therapy, particularly with regard to prostate health, are being addressed, and ongoing research should provide more insight into overall treatment goals and threshold effects.

Until the true risk of testosterone therapy is documented in long-term studies, it is clinically and ethically important to evaluate patients’ signs and symptoms—including performing a DRE of the prostate and measuring hematocrit and PSA—at baseline before initiating testosterone therapy and to monitor the prostate during testosterone therapy. Symptomatic hypogonadal men should be treated with testosterone therapy, and their symptoms, prostate, hematocrit, and PSA should be monitored at 3 and 12 months and then annually.


Proceedings From the TU 1st Annual Conference on Improving Clinical Outcomes in Hypogonadism

1. Letter From the Co-Chairs
   Glenn R. Cunningham, MD, and Ridwan Shabsigh, MD

2. CME Accreditation Information

4. Introduction

4. Epidemiology of Hypogonadism
   Glenn R. Cunningham, MD

5. Diagnosis and Management of Hypogonadism and Associated Chronic Comorbid Conditions
   From the Primary Care Perspective
   Richard Sadovsky, MD

7. Laboratory Diagnosis of Hypogonadism: The Clinical Imperative
   Shalender Bhasin, MD

8. Hypogonadism Treatment Considerations, Monitoring, and Follow-up
   Adrian S. Dobs, MD, MHS

10. Novel Testosterone Formulations and Dosing: Potential Impact on Treatment and Outcomes
    Ajay Nehra, MD

12. Testosterone Therapy and the Prostate: Evaluating the Evidence
    Leonard N. Marks, MD

13. Testosterone and the Prostate: What Is the Relationship?
    Abraham Morgentaler, MD

14. Monitoring and Treatment After Prostatectomy or Brachytherapy
    E. David Crawford, MD

16. Conclusion

17. References