

# Endocrine Society

## Conference Courier Highlights Report on Hypogonadism



# Introduction

The treatment of hypogonadism is always a major topic at the annual meeting of the Endocrine Society, and this year's meeting, held June 10 to 13, 2009, in Washington, DC (ENDO 2009), was no exception. Hypogonadism is a clinical condition defined as abnormally low levels of testosterone in the presence of one or more symptoms associated with androgen deficiency.<sup>1-4</sup> The purpose of this Conference Courier is to briefly review some basic information and the newest data on hypogonadism and its treatment as presented at ENDO 2009.

## Issues in the Diagnosis and Management of Hypogonadism

### Questions in Male Reproductive Health

#### **Are Men Losing Their Gonads (and Does It Matter)?**

During a symposium on Wednesday, André B. Araujo, PhD (New England Research Institutes [NERI], Watertown, MA), spoke about the importance of epidemiologic studies for providing unbiased data on the distribution and determinants of disease that cannot be obtained by clinical trials.<sup>5</sup> Dr Araujo reviewed the epidemiologic data on endocrine function in aging men, with a particular focus on changes in serum testosterone concentrations and their potential impact on men's overall health. Briefly, epidemiologic studies worldwide have demonstrated that endogenous testosterone falls and luteinizing hormone (LH) increases with age, suggesting primary testicular failure—

ie, aging men *are* losing their gonads. In obese men, testosterone also falls but LH does not change, suggesting a hypothalamic/ pituitary cause—ie, obese men are *not* losing their gonads. Epidemiologic studies have also shown that low levels of testosterone are associated with important health issues, including muscle and bone loss, increasing fat mass, cardiometabolic risk, and premature mortality. However, reductions in testosterone are modified by health and lifestyle, as well as age. One caveat for all studies is that “who you study can determine what you find.” For anyone interested in more detail, Dr Araujo's slide presentation (slides only) is available at: <http://www.neriscience.com/web/documents/Araujo%20Are%20Men%20Losing%20Their%20Gonads.ENDO.2009.final.web.pdf>.

# Topics in Male Hypogonadism

Important and controversial issues in the diagnosis and treatment of male hypogonadism were presented early Wednesday morning at an industry-sponsored (Solvay Pharmaceuticals, Inc., Marietta, GA) CME breakfast symposium chaired by Bradley D. Anawalt, MD (University of Washington Medical Center, Seattle). Testosterone levels decrease and the prevalence of symptomatic hypogonadism increases with increasing age. Treatment with exogenous testosterone increases strength and muscle mass, bone mineral density (BMD), overall sense of well-being, and mood. The most common adverse effects are acne in younger men and erythrocytosis, which is more common in older men. Increases in protein-specific antigen (PSA) values and prostate volume and decreases in high-density lipoprotein (HDL) values have been reported. Undertreatment of hypogonadism results in part from the perception that the risks, particularly the risk of prostate cancer, outweigh the benefits.<sup>6</sup> In addition, diagnosis of hypogonadism is fraught with difficulties and challenges. The speakers addressed 3 controversial questions: How do we diagnose hypogonadism? Is testosterone good for the heart? Is testosterone bad for the prostate?

## **Difficulties in the Diagnosis of Male Hypogonadism**

Total testosterone (TT) is currently the recommended initial test for diagnosis of hypogonadism,<sup>1,3</sup> but controversy exists as to whether the free-testosterone (FT) fraction or bioavailable

testosterone (free plus albumin-bound testosterone [BioT]) might be more biologically relevant, and the guidelines are vague on this topic. Robert I. McLachlan, MD, PhD (Prince Henry's Institute of Medical Research and Monash University, Melbourne, Australia), reviewed the issues and evaluated the evidence for and against FT as the preferable test for diagnosing and monitoring hypogonadism. The issue is complex, and this was an extensive and evidence-based review. Because of space limitations, only the final conclusions can be summarized here:

- Diagnosis should be made on the basis of both testosterone levels and symptoms
- BioT is very method-dependent, and reference ranges are not available
- The superiority of FT over TT has not been confirmed, and TT may correlate better with symptoms than FT or BioT
- Make diagnoses based on symptoms and TT values, using the best available methods for measuring TT (the gold standard is mass spectrometry). Limit use of FT to settings associated with perturbations of sex hormone-binding globulin (SHBG) when testosterone is not diagnostic (eg, obesity, insulin resistance, liver disease, drug abuse), but be aware of the thin evidential base for its use
- Many methods are available for obtaining FT, but calculated FT (cFT) is the most appropriate in this setting. Unfortunately, there is no universally accepted method of calculating FT
- Because cFT ultimately depends on TT, it would be useful to improve methods for measuring TT and to standardize assays and reference ranges

### Is Testosterone Bad for the Prostate?

Stephanie T. Page, MD, PhD (University of Washington Medical Center, Seattle), addressed this important question. The prostate is indisputably an androgen-responsive tissue: Androgens are necessary for prostate development, correction of hypogonadism increases prostate size and PSA, and prostate cancer responds to testosterone withdrawal. However, the incidence of prostate disease increases over a man's lifetime as testosterone levels fall. The active androgen in the prostate is dihydrotestosterone (DHT), and emerging molecular data suggest that exogenous testosterone therapy and the resulting increased serum testosterone concentrations have little effect on the prostate.

There is little evidence that exogenous testosterone therapy increases the risk that prostate cancer will develop. Testosterone therapy in older hypogonadal men had minimal effects on prostate tissue, hormones, and gene expression,<sup>7</sup> and supraphysiologic doses did not increase PSA.<sup>8</sup> The incidence of prostate cancer appears to be reduced by 5 $\alpha$ -reductase inhibitors (5 $\alpha$ RIIs), but their role in clinically significant prostate disease is as yet unclear. Prostate health should be monitored at baseline and routinely during treatment, according to guidelines (Table 1).<sup>1</sup> Many experts believe, and some evidence indicates, that patients who have been successfully treated for prostate cancer may be safely and effectively treated with exogenous testosterone for hypogonadism. Dr Page warned, however, that patients with a history of prostate cancer should be treated cautiously, only when there is a clear need and goal for therapy, and in a clinical trial, if possible.

**Table 1. Recommendations for Routine Prostate Monitoring During Exogenous Testosterone Therapy<sup>1</sup>**

- Measure PSA and perform DRE at baseline
- Patients with PSA >3.0 ng/dL should be referred for urologic evaluation before beginning therapy
- Check PSA and perform DRE before starting treatment, at 3 months, and then in accordance with prostate cancer screening guidelines, depending on patient's age and race
- Obtain urologic consultation if there is:
  - A verified serum PSA concentration >4.0 ng/mL
  - An increase in serum PSA concentration >1.4 ng/mL within any 12-month period of testosterone treatment
  - A PSA velocity of >0.4 ng/mL•y using the PSA level after 6 months of testosterone administration as the reference (only applicable if PSA data are available for a period exceeding 2 y)
  - Detection of a prostatic abnormality on DRE
  - An American Urological Association or International Prostate Symptom Score of >19

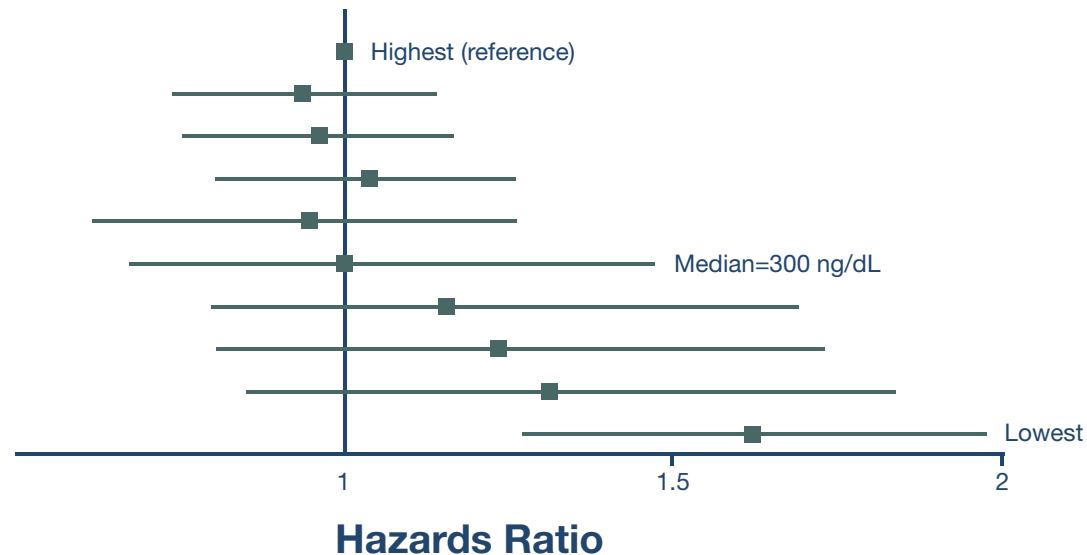
DRE, digital rectal examination; PSA, prostate-specific antigen.  
Adapted with permission.

### Is Testosterone Good for the Heart?

After a thorough review of the literature, Frances J. Hayes, MB, FRCPI (University College Dublin School of Medicine, Dublin, Ireland), concluded that low endogenous testosterone levels are associated with an increased risk of cardiovascular disease (CVD), cardiovascular and all-cause mortality (Figure 1),<sup>9</sup>

metabolic syndrome, and type 2 diabetes via a direct effect on body composition and insulin sensitivity. The available data from epidemiologic and small interventional studies suggest that exogenous testosterone therapy has favorable effects on coronary vasculature and surrogates of coronary artery disease (CAD), but definitive studies are needed to confirm the data and to determine whether these effects will translate into a reduction in myocardial infarction (MI) and cardiovascular mortality.

**Figure 1. All-Cause Mortality According to Deciles of TT, Adjusted for Age, BMI, Waist-to-Hip Ratio, Current Smoking, Alcohol Use, and Exercise<sup>9</sup>**



Squares represent point estimates for hazard ratios; lines indicate 95% confidence intervals.

Median TT values for deciles 1 to 10: 171, 209, 241, 266, 288, 314, 338, 370, 422, and 507 ng/dL, respectively.

BMI, body mass index; TT, total testosterone.

Reproduced with permission.

Later in the day, Carolyn A. Allan, MBBS(Hons), PhD (Prince Henry's Institute, Clayton, Australia), gave a similar presentation, also titled *Is Testosterone Good for the Heart?*<sup>10</sup> Obesity, particularly abdominal obesity, is an important confounder in interpreting the data on exogenous testosterone therapy and CVD, and more studies are needed. In brief, supraphysiologic levels of testosterone are not cardioprotective and are probably harmful, and abnormally low levels of testosterone constitute an important risk factor for CVD. No adverse cardiovascular events have been demonstrated, however, at normal eugonadal

levels of testosterone. Because age, obesity, and lifestyle affect testosterone concentrations, it is not clear whether exogenous testosterone therapy alone will affect the broader health outcomes. Dr Allan concluded that normal testosterone levels are good for the male heart and are, in fact, a marker for cardiovascular health. Therefore, current evidence indicates that for men with clear hypogonadism (symptoms and indisputably low testosterone), testosterone therapy need not be withheld because of concerns about adverse cardiovascular effects. However, the cardiovascular effects, if any, of treating older men with more modest declines in serum testosterone levels are uncertain.

## Symposium: Male Hypogonadism and Its Management (Can the Nut Be Cracked?)

Interest in issues and challenges involved in the diagnosis and management of hypogonadism was evidenced by the standing-room-only crowd who attended this symposium, chaired by J. Lisa Tenover, MD, PhD (Emory University School of Medicine, Atlanta, GA), on Saturday to hear presentations by Robert I. McLachlan, MD, PhD (Prince Henry's Institute of Medical Research and Monash University, Melbourne, Australia); Andrea D. Coviello, MD (Boston University School of Medicine, Boston, MA); and Joel S. Finkelstein, MD (Massachusetts General Hospital, Boston, MA).

### **The Free Testosterone Hypothesis: Is It Liberating?**

Dr McLachlan again reviewed the evidence for and against FT.<sup>11</sup> (See preceding section, *Difficulties in the Diagnosis of Male Hypogonadism.*)

### **Age-Related Differences in Response to Testosterone Therapy: The Influence of Metabolic Clearance**

Younger men tolerate and respond to exogenous testosterone therapy better than older men.<sup>12</sup> A metaanalysis of adverse events in 19 placebo-controlled studies found the incidence of erythrocytosis among older men ( $\geq 45$  y of age) to be 4 times higher in treated men than untreated men.<sup>13</sup> Although all prostate events were significantly more common among treated men than untreated men, the incidences of prostate cancer, prostate biopsies, and PSA values  $>4$  ng/mL were numerically but not statistically significantly higher. The effect of treatment on cardiovascular events was neutral or slightly favorable, and the mortality rate and incidence of sleep apnea were similar.

Dose-response studies with exogenous testosterone have found that symptomatic efficacy is dose-related and equivalent in older and younger men, despite the fact that, for a given dose, serum TT levels are higher (Figure 2) and adverse events more common and more serious in older than in younger treated men.<sup>8,14,15</sup>

A study to elucidate the mechanism for the higher testosterone levels in older men found that hepatic clearance decreased with age and, although the normal curves overlapped substantially, was 24% lower in older men than in younger men (1391±69 vs 1821±102 L/d,  $P=.007$ ).<sup>16</sup> In multiple regression models, the metabolic clearance rate of testosterone was predicted by lean body mass ( $P=.008$ ), percent fat mass ( $P=.009$ ), and SHBG ( $P=.001$ ). Based on these data, Dr Coviello recommended starting older men at lower doses of exogenous testosterone, monitoring frequently for efficacy and adverse events, and titrating as appropriate.<sup>8</sup>

#### **How Much Testosterone Does a Man Need for Sex and Muscle?**

Reference ranges for low testosterone are currently based on a statistical distribution rather than physiology. Low testosterone concentrations are associated with many physiologic changes. Recently, the concept that different testosterone-supported functions may require different levels of testosterone has been gaining acceptance, but the concentrations of testosterone required to support these functions are not known. Dr Finkelstein presented, to a packed audience, the results of research conducted to help answer that question.<sup>17</sup> Testosterone was clamped by administration of a gonadotropin-releasing hormone (GnRH)

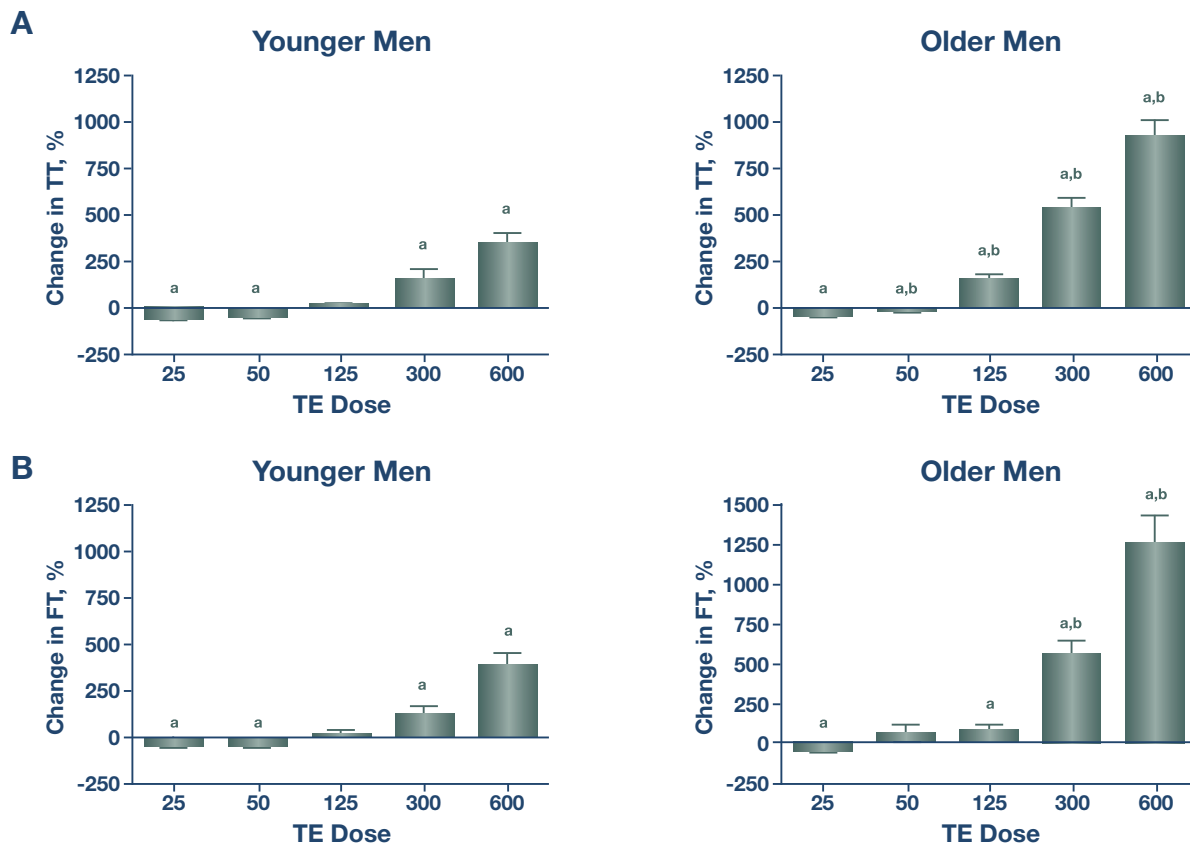
agonist in healthy eugonadal men at levels ranging from prepubertal to high-normal. Subjects between 20 and 50 years of age were randomly assigned to 6 dosing groups. Groups 1 to 5 received gosereline acetate (GA) 3.6 mg every 4 weeks for 16 weeks plus placebo gel, 1.25 g gel, 2.5 g gel, 5 g gel, or 10 g gel; group 6 received double placebo. Data were analyzed by baseline and postclamping testosterone levels. Mean ( $\pm$ SE) serum TT levels during treatment were 44±2, 187±11, 332±29, 538±33, 829±60, and 584±29 ng/dL in groups 1 to 6, respectively. A linear dose response was noted for TT, FT, and BioT but not for estradiol ( $E_2$ ). The results showed:

- Overall a strong but distinct dose-response relationship between testosterone and androgen-related outcomes was demonstrated
- Erectile function was maintained until TT fell below 100 ng/dL
- Libido increased progressively across treated groups
- PSA began to decrease when TT fell below baseline but did not increase at levels above baseline (see also Pallais et al<sup>18</sup>)
- Bone resorption markers increased when TT fell below 200 ng/dL
- Total fat mass began to increase when TT fell below 400 ng/dL; lean mass was preserved until TT fell below 100 ng/dL
- Abdominal fat did not change in a dose-response manner

Thus, maintenance of body composition required moderate levels of testosterone.

These results indicate that intervention thresholds may depend on the target organ, tissue, or process being considered.

**Figure 2. (A) Percent Change in Serum TT From Baseline to Treatment (Mean of Days 84 and 113 TT in Younger and Older Men by Dose Group) and (B) Percent Change From Baseline of Serum FT (Mean of Days 84 and 113 FT in Younger and Older Men by Dose Group)<sup>16</sup>**



(A) TT showed a linear dose-response relationship (mean percent change from baseline, ANOVA,  $P < .0001$  for both younger and older men).

(B) FT showed a linear dose-response relationship (mean percent change from baseline, ANOVA,  $P < .0001$  for both younger and older men).

<sup>a</sup>Statistically significant change from baseline,  $P < .05$ .

<sup>b</sup>Significant difference in percent change from baseline comparing younger and older men.

ANOVA, analysis of variance; FT, free testosterone; TE, testosterone enanthate; TT, total testosterone.

Reproduced with permission.

## Meet-the-Professor Sessions

Frances J. Hayes, MB, FRCPI (University College Dublin School of Medicine, Dublin, Ireland), led a session on diagnosing hypogonadotropic hypogonadism (HH), with a focus on idiopathic HH (IHH), and determining an appropriate, individualized therapy.<sup>19</sup> Key points that Dr Hayes made during this well-attended and highly interactive session included the importance of going through all the steps for differential diagnosis, because adult-onset IHH is a diagnosis of exclusion, and the importance of classification as primary or secondary hypogonadism, because the cause and treatment are different. The cause of HH may be structural (eg, from tumors, brain damage, infections), functional (eg, from systemic illness, weight loss, medications), or genetic (eg, IHH, Kallmann syndrome, congenital adrenal hypoplasia, mutations in gonadotropin). Appropriate diagnosis requires a detailed history and physical examination, measurement of serum testosterone concentrations, and measurement of gonadotropin concentrations to determine the level of the defect in the hypothalamic-pituitary-gonadal (HPG) axis (ie, whether it is primary hypergonadotropic or secondary hypogonadotropic). Diagnosis should also rule out involvement of more than the HPG axis and include an evaluation of other anterior pituitary hormones (if cortisol level <18 µg/dL, an insulin tolerance test or corticotropin stimulation test should be performed) and thyroxine level for patients with secondary hypothyroidism, because thyrotropin levels may be normal. Also, prolactin level and iron studies should be done to exclude prolactinoma and hemochromatosis, respectively. Magnetic resonance imaging of the hypothalamic-pituitary region is needed to exclude a tumor.

A bone density scan, although not diagnostic, is useful. Management options are decided jointly by the patient and physician after consideration of all the options. Key factors in determining management are whether puberty has occurred normally and whether the patient wants to preserve fertility.

In another highly interactive session, Mark Palmert, MD, PhD (University of Toronto, Department of Pediatrics, Toronto, Ontario), discussed the management of delayed puberty in children with the aid of two case studies, one of a boy and one of a girl, each aged 14.5 years.<sup>20</sup> Delayed puberty is most commonly due to constitutional delay of growth and maturation, but other causes must be considered. Many factors influence if, when, and how to treat hypogonadism in children, and there is no “right” answer. For delayed puberty in boys, measurement of testosterone is not useful; diagnosis is made on an examination of secondary sexual characteristics. Therapeutic dosages of testosterone have not been established specifically for children and adolescents. Very few of the physicians who attended this session use gels or patches in this age group; most use injectable testosterone cypionate (TC)/testosterone enanthate (TE). Dr Palmert uses TC/TE 50 mg IM for 3 months, reassesses 1 month after the last dose, and repeats the injections for up to 1 year at no more than 100 mg/mo if no development has occurred. If there is no response after 1 year, he considers another diagnosis. Later in the patient’s life, spermatogenesis and testicular development may be achieved with gonadotropin therapy, if desired. Treatment regimens for delayed puberty in girls are both more varied and more controversial than those for boys. Conjugated equine estrogens are commonly employed, but oral, injectable, and transdermal estradiol are available and have been used. For permanent HH in boys or girls, doses are gradually increased over 2 to 3 years to adult doses and dosing intervals.

Vincenzo Rochira, MD, PhD (Department of Medicine, Endocrinology & Metabolism, Geriatrics, University of Modena & Reggio Emilia, Italy), discussed clinical issues in the management of Klinefelter syndrome.<sup>21</sup> Klinefelter syndrome is one of the most common chromosomal abnormalities, occurring in 1 of every 500 to 600 births. The Klinefelter syndrome phenotype depends on genetics (eg, mosaicism, incomplete penetrance), age, and hormonal levels and varies widely. Only 25% to 50% of men with Klinefelter syndrome receive an appropriate diagnosis and, often, not until later in life. A multidisciplinary

approach during genetic counseling decreases the pregnancy termination rate and improves management. Hypogonadism is common in men with Klinefelter syndrome and can be successfully treated with exogenous testosterone therapy just as it can in other hypogonadal men. Testosterone therapy for adolescents is problematic because of decreased spermatogenesis and requires careful counseling; however, treatment is usually unnecessary because men with Klinefelter syndrome often have sufficient testosterone to permit the onset and progression of puberty. Testosterone does not affect gynecomastia, which requires surgery. Data are conflicting on whether men with Klinefelter syndrome have higher-than-normal serum E<sub>2</sub> levels.

## Diagnosis and Treatment of Borderline Hypogonadism in Aging Men

In a Case Management Forum, Frederick Wu, MD, FRCP, presented an overview of the significance of androgen deficiency in the aging male and then discussed 3 case studies.<sup>22</sup> Late-onset hypogonadism (LOH) differs from other types of hypogonadism and may have mixed causes. Functional changes in the HPG axis result in decreased spermatogenesis and LH pulse amplitude and increased or normal LH and follicle-stimulating hormone. Concentrations of endogenous serum TT decrease with age (Figure 3)<sup>23</sup> at the rate of approximately 1% per year after 40 years of age. FT also decreases with age, although SHBG increases by 1.3% per year after age 40. TT levels between 250 and 345 ng/dL are considered borderline. If TT levels are borderline, testing should be repeated.

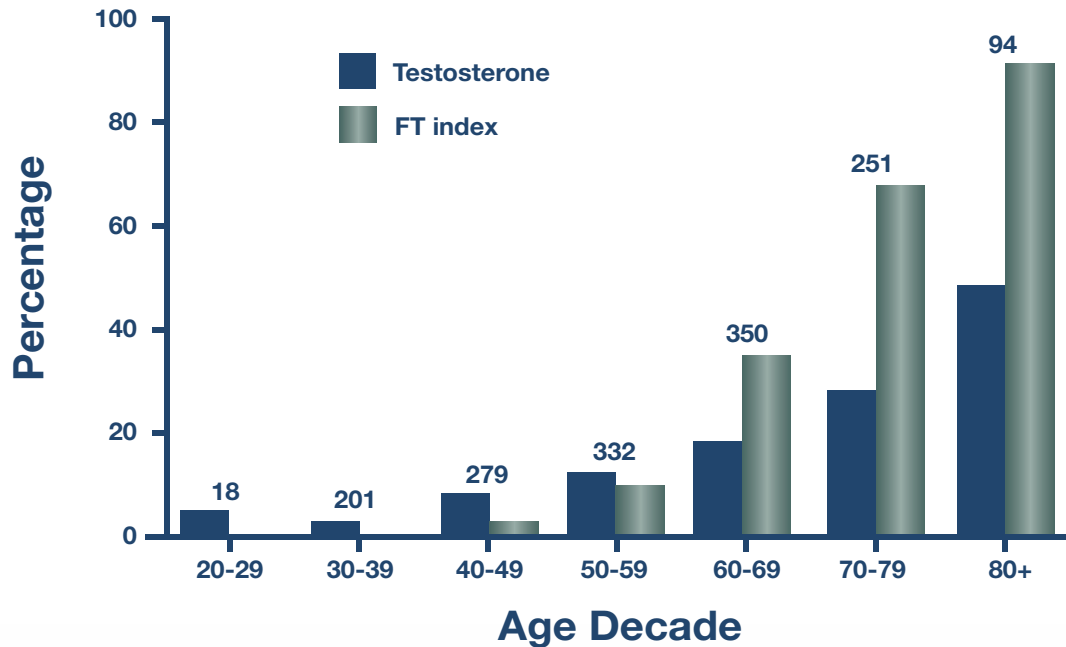
The benefits of treatment for hypogonadism in general are supported by evidence, but data are as yet inadequate to prove efficacy and safety specifically in LOH. Key points that were made during discussion of the case studies include:

- A decrease in testosterone levels with age is not inevitable, and interpatient variability is wide
- Measurement of FT may be useful for men with borderline TT levels, but it is important to remember that experience is limited and reference ranges are often not available
- The risk of polycythemia is increased with testosterone therapy, particularly in older men, and with the injectable shorter-acting products

- Treatment options other than testosterone (eg, lifestyle changes, antiestrogens, aromatase inhibitors) are available that are not associated with the same risks
  - Lifestyle changes alone (eg, exercise, weight loss) can increase testosterone levels and decrease symptoms and are a good first management option
- Epidemiologic data show no association between testosterone treatment and prostate cancer, but the evidence is not yet definitive

- PSA is a nonspecific marker, and increases in PSA values may be due to many factors
- A risk calculator to assess the lifetime risk of prostate cancer development may be helpful in making treatment decisions; the calculator is available at: <http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp>
- For patients with elevated PSA values but no evidence of prostate cancer, special precautions should be taken at baseline and monitoring done according to the guidelines

**Figure 3. Age-Related Decrease in Serum TT and FT Index<sup>23</sup>**



FT, free testosterone; TT, total testosterone.  
Reproduced with permission.

# Broadening Spectrum of Hypogonadotropic Hypogonadism

At an industry-sponsored (Genentech, Inc., South San Francisco, CA) symposium on Thursday chaired by Nelly Mauras (Nemours Children's Clinic, Jacksonville, FL), William F. Crowley Jr (Massachusetts General Hospital and Harvard Medical School, Boston, MA) provided a historical overview and update on progress in determining the underlying cause(s) of and identifying genes involved in congenital idiopathic hypogonadotropic hypogonadism (cIHH), or testosterone/GnRH deficiency.<sup>24</sup> He also discussed the significance of new data on spontaneous neuroendocrine and gonadal reversal of cIHH.<sup>25</sup> Congenital IHH is caused by an isolated defect in GnRH release, action, or both. The men who had a reversal had few commonalities: Testosterone levels and duration of treatment varied widely; some received only GnRH,

whereas others received both GnRH and exogenous testosterone; some had Kallmann syndrome, and others were normosmic. All the reversals were identified within 3 to 9 weeks after discontinuation of therapy. Sequencing of family groups showed variable expressivity of the same mutation. Reversals occurred despite the lack of an olfactory bulb in some patients. Biologically, spontaneous reversals of IHH indicate that the GnRH network is in place and that there may be another source of GnRH neurons. Clinically, the fact that reversals occur in 10% to 15% of cases holds out hope for men. It also indicates that physicians should monitor testicular size and prompts the question whether spontaneous reversals will occur in other releasing-factor deficiencies. Dr Crowley concluded that loss of function mutations is responsible for severe GnRH deficiency and proposed a gene-environment interaction.

# Original Research

## Hypogonadism and Men's Health

Using cross-sectional baseline data on 3369 men (mean age, 60±11 y) from the European Male Ageing Study (EMAS), Corona et al investigated the relationship between LOH, general health, and sexual function.<sup>26</sup> Hypogonadism was defined as TT <10.4 nmol/L (<300 ng/dL). More than half of the subjects had one or more age-associated comorbidities, the most common being hypertension (29%), heart disease (16%), prostate disease (12%), and diabetes (8%). Approximately 30% of subjects reported erectile dysfunction (ED), but only 38% of those men were concerned about it. Overall, the prevalence of LOH was 13.2%, and prevalence increased with increasing age. General health (particularly diabetes, CVD, lower urinary tract infections, and depression) predicted ED but was only modestly associated with LOH. General health and depression were associated with both LOH and low sexual activity, but only depression and LOH were associated with decreased sexual desire.

### **Hypogonadism and Insulin Resistance/Sensitivity**

Although hypogonadism is significantly more prevalent among men with type 2 diabetes than in the general population, it is not yet clear whether endogenous testosterone or testosterone therapy is correlated with insulin sensitivity/resistance, because study results have been inconsistent.<sup>1,3,27-30</sup> As part of the Odense Androgen Study, Frederiksen et al evaluated pretreatment insulin sensitivity by the euglycemic-hyperinsulinemic clamp method in 60 men aged 60 to 78 years with BioT <7.4 nmol/L and waist circumferences >94 cm (37 in).<sup>31</sup> Insulin sensitivity was not associated with endogenous testosterone levels after adjustment for total or central fat mass.

### **Hypogonadism and Metabolic Syndrome**

Low testosterone concentrations are more prevalent in men with metabolic syndrome than in the general population.<sup>32-34</sup> In the first such epidemiologic study conducted in Turkey, 30% of men older than 60 years with metabolic syndrome (n=30) had LOH compared with 13% of age-matched healthy controls (n=30), although the difference did not reach statistical significance.<sup>35</sup> The levels of TT and SHBG were significantly lower ( $P=.004$  and  $P=.003$ , respectively) in the metabolic syndrome group than in the control group. An inverse association was noted between TT and the components of metabolic syndrome, except for HDL and fasting glucose levels. Metabolic syndrome was diagnosed according to the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults (ATP III) criteria.

### **Hypogonadism and Diabetes**

In a cross-sectional study from Singapore, 188 men (mean age, 55.5 y) were evaluated to determine whether androgen deficiency is associated with cardiovascular risk in aging men and whether TT or SHBG better predicts metabolic syndrome.<sup>36</sup> Sixty-five men had metabolic syndrome according to National Cholesterol Education Program ATP III 2005 criteria. Framingham risk scores were calculated for all subjects. The number of fulfilled parameters for metabolic syndrome correlated negatively with TT ( $r=-0.03$ ,  $P<.001$ ) and SHBG ( $r=-0.31$ ,  $P<.001$ ), and after adjustment for age and creatinine, only low levels of SHBG predicted development of metabolic syndrome. Framingham risk scores correlated with the number of metabolic syndrome components but not with TT or SHBG. The men with metabolic syndrome had significantly lower TT (14.9 vs 16.6 nmol/L,  $P=.019$ ) and SHBG (34.1 vs 40.8 nmol/L,  $P=.005$ ) values and significantly higher Framingham risk scores (5.75 vs 4.5,  $P=.001$ ) than the men without metabolic syndrome.

Approximately one third of men with type 2 diabetes have HH (FT <0.174 nmol/L or cFT <0.225 nmol/L).<sup>37</sup> Dandona et al measured serum testosterone, SHBG, and E<sub>2</sub> concentrations and calculated FT and free E<sub>2</sub> in 98 men with type 2 diabetes to determine whether aromatase activity in the adipose tissue of obese men increases the conversion of testosterone to E<sub>2</sub>.<sup>38</sup> The concentrations of E<sub>2</sub> were not significantly different between the two groups or between the obese and nonobese men. For obese

and nonobese men with type 2 diabetes, total E<sub>2</sub> values were 5.1±0.04 and 6.1±0.5 ng/dL, respectively ( $P=.1$ ); free E<sub>2</sub> values were 0.099±0.008 and 0.104±0.013 ng/dL, respectively ( $P=.8$ ). Upon multiple regression analyses, the only predictor of FT and total E<sub>2</sub> concentrations was SHBG. The authors did not specify which type of E<sub>2</sub> assay was used. Thus, other mechanisms must account for suppression of the HPG axis in diabetic men.

### **Hypogonadism, Cardiovascular Disease, and Mortality**

Low serum testosterone concentrations have been associated with an increased risk of CVD and higher cardiovascular and all-cause mortality rates.<sup>39,40</sup> Several studies presented at ENDO 2009 assessed metabolic and cardiovascular risk. Study populations varied widely, and the results were inconsistent.

A large study (N=930) in the United Kingdom assessed the effect of endogenous TT and BioT on survival of men over a period of 6.9±2.1 years.<sup>41</sup> Mean age at baseline was 60.8 years. The overall prevalence of testosterone deficiency in the CHD group was 20.9% using BioT <2.6 nmol/L, 16.9% using TT <8.1 nmol/L, and 24% using either. The mortality rate was significantly higher in the androgen-deficient group than in the eugonadal group (21% vs 12%,  $P=.002$ ). TT <15.1 nmol/L and BioT <2.6 nmol/L were each independently associated with all-cause mortality ( $P=.03$  and  $P<.0001$ , respectively) and cardiovascular mortality ( $P=.02$  and  $P=.007$ , respectively). The authors concluded that TT is less specific than BioT and that BioT (or FT) is preferable for assessing androgen deficiency and the risk of death.

Among a randomly selected cohort of 1568 men from the general population who participated in the fourth Tromsø study (1994-1995) in Norway, FT values in the lowest quartile (<158 pmol/L)—but not TT—were associated, independently and significantly, with increased risk of all-cause mortality compared with FT values in the higher quartiles (hazard ratio [HR], 1.24; 95% confidence interval [CI], 1.01-1.53) after age adjustment and upon multivariate analysis (HR, 1.24; 95% CI, 1.01-1.54).<sup>42</sup> Men in the lowest FT quartile had more MIs, but the difference was not statistically significant.

Callou et al evaluated the relationship between endogenous sex hormones and CAD among patients aged 40 to 70 years who had been referred for coronary angiography; baseline characteristics and laboratory and clinical measurements of case subjects and controls were similar.<sup>43</sup> The 54 case subjects had CAD, defined as  $\geq 70\%$  occlusion of at least one major artery; the 59 control subjects had <50% occlusion of any major artery. Only  $E_2$  was significantly more common in the case subjects than in controls ( $P=.006$ ). Concentrations of TT, FT, BioT, and SHBG were not significantly different between groups.

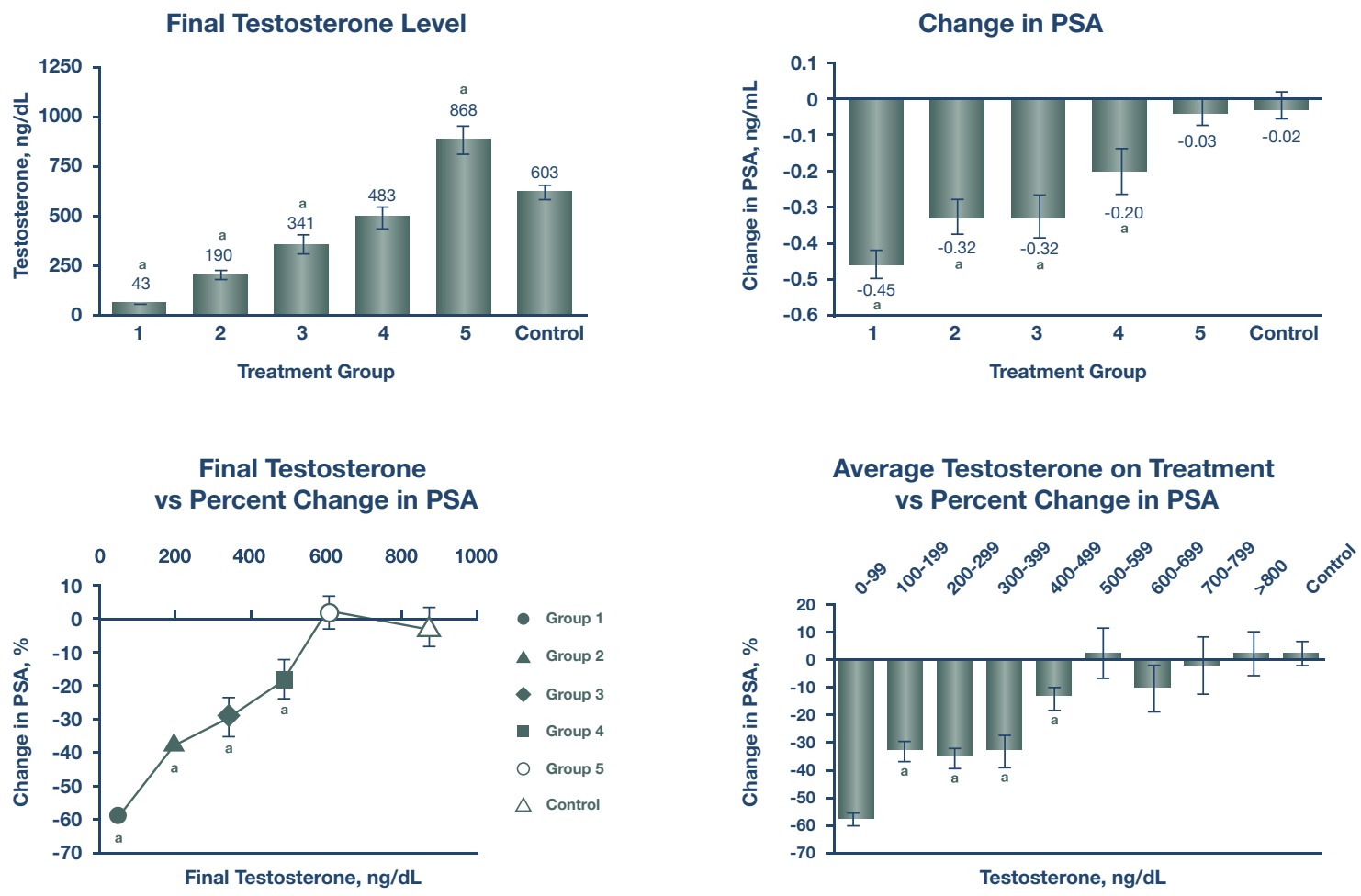
To clarify the effects of endogenous male sex hormones on vascular function in relation to the pathogenesis of atherosclerosis, a small Turkish study measured the vascular reactivity of young male patients with HH and no cardiovascular risk factors compared with that of age-matched healthy controls ( $N=51$ ; mean age, 21 y).<sup>44</sup> Flow-mediated dilatation (FMD) and endothelium-independent dilatation (EID) induced by sublingual nitroglycerin were significantly higher in the case subjects than in controls (13% vs 8%,  $P=.003$ ;

21% vs 15%,  $P=.023$ ). EID did not correlate independently with male sex hormones; vascular reactivity measured by ultrasound of the right brachial artery; or vessel diameter at rest either during reactive hyperemia (endothelium-dependent FMD) or after sublingual nitroglycerin (EID). Only serum HDL levels and baseline vessel diameter were independently associated with FMD values (relative risk [RR], 3.21; 95% CI, 0.14-0.63;  $P=.003$ , and RR, -3.20; 95% CI, -18.00 to -4.02;  $P=.003$ , respectively). The authors concluded that endogenous male sex hormones seem to exert negative effects on vascular reactivity and that much of their effect may be indirect via alteration of lipid profiles.

#### **Hypogonadism and the Prostate**

In an oral presentation chaired by Glenn R. Cunningham, MD (Baylor College of Medicine, Houston, TX), and Adrian Dobs, MD, MHS (Johns Hopkins University School of Medicine, Baltimore, MD), J. Carl Pallais, MD, MPH (Harvard Medical School, Boston, MA), presented results of research conducted at Massachusetts General Hospital and Harvard Medical School to explore the relationship between PSA and endogenous testosterone in healthy men by inducing hypogonadism with a GnRH agonist and then treating with various doses of testosterone gel.<sup>18</sup> Subjects between 20 and 50 years of age were randomly assigned to 6 dosing groups. Groups 1 to 5 received GA 3.6 mg every 4 weeks for 16 weeks plus placebo gel, 1.25 g gel, 2.5 g gel, 5 g gel, or 10 g gel; group 6 received double placebo. PSA levels changed in a stepwise, dose-response manner (Figure 4). A similar pattern was seen for DHT, but FT and BioT were not associated with PSA changes. Stratification by testosterone levels showed that PSA decreased when testosterone values fell below baseline (mean,  $529 \pm 154$  ng/dL) but did not change when testosterone levels rose into the high-normal range. Thus, at least in the short term, PSA is more sensitive to androgen deficiency than to androgen excess in young men.

**Figure 4. PSA Levels Change by Testosterone Levels in a Dose-Response Manner up to Approximately 500 ng/dL and Then Stabilize<sup>18</sup>**



<sup>a</sup>P<.05 vs control.  
 PSA, prostate-specific antigen.  
 Reproduced with permission.



# Benefits of Exogenous Testosterone Therapy

## Body Composition

Increase in lean body mass is a known benefit of testosterone therapy.<sup>1</sup> A randomized, placebo-controlled study was conducted to determine whether augmentation of testosterone and growth hormone/insulin-like growth factor-1 (GH/IGF-1) to youthful levels would enhance muscle strength as well as muscle mass in older men.<sup>45</sup> Subjects (N=122) aged 65 to 90 years with baseline testosterone concentrations of 150 to 550 ng/dL and IGF-1 values in the lowest tertile were given a long-acting GnRH agonist to prevent endogenous testosterone secretion by Leydig cells, then prescribed daily testosterone gel 5 mg or 10 mg plus recombinant human growth hormone at 0, 3, or 5 mg/kg. Lean body mass increased significantly at weeks 8 and 17. Total appendicular skeletal muscle mass increased significantly at weeks 8 and 17 except in the two lowest dosage groups (testosterone 5/GH 0, testosterone 5/GH 3). In contrast, improvements in composite strength were predominantly seen only at week 17, suggesting that increases in muscle mass at week 8 may have been due to water retention rather than accrual of myofibrillar protein. Evaluation of total body water by deuterium oxide dilution at week 17 showed minimal effects on hydration. Thus, an increase in lean body mass at 17 weeks, but not at 8 weeks, was associated with increased skeletal mass and muscle strength, probably due to accrual of functional skeletal muscle protein. The investigators recognize that interpretation of the study is limited by the lack of total body water data at week 8.

## Insulin Resistance, Metabolic Syndrome, and Diabetes

A study conducted in Russia and the United Arab Emirates with Bayer Schering Pharma examined glycemic status and changes in antihypoglycemic therapy in 18 men with androgen deficiency (FT <250 pmol/L; TT <12 nmol/L) and metabolic syndrome and/or type 2 diabetes who received intramuscular testosterone undecanoate (TU) for 102 weeks (range, 72-132 wk).<sup>46</sup> Six men were taking insulin, and 12 were taking antihypoglycemic medications. Correction of androgen deficiency improved glycemic parameters and allowed discontinuation of insulin in 3 men. The degree of diabetic compensation depended on the duration of treatment (data not shown).

Men with metabolic syndrome or some of its components have a higher prevalence of hypogonadism than the general population.<sup>47</sup> Hepatic steatosis (nonalcoholic fatty liver disease, or NAFLD) is an important factor in the pathogenesis of metabolic syndrome, is correlated with all components of metabolic syndrome, and is now considered the hepatic manifestation of metabolic syndrome.<sup>48-50</sup> Approximately 90% of patients with NAFLD have >1 and one third have  $\geq 3$  features of metabolic syndrome.<sup>51</sup> Cytokines secreted by visceral adipocytes may depress peripheral insulin-mediated glucose uptake and increase hepatic fat accumulation. Previously, Haider et al reported the effects of intramuscular TU 1000 mg in 117 hypogonadal men (5.9-12.1 nmol/L, 34-69 years of age) for 12 months on variables of metabolic syndrome and on liver enzymes (aspartate aminotransferase/alanine aminotransferase [AST/ALT]) and C-reactive protein (CRP).<sup>52</sup> CRP is a  $\beta$ -globulin (acute-phase protein) synthesized by the liver and found in the serum of persons with certain inflammatory diseases. A poster presented at ENDO 2009 provided expanded data for 122 men from a private urology practice in Germany who received

testosterone therapy for 24 to 30 months.<sup>53</sup> Normalization of the men's plasma testosterone levels significantly improved features of metabolic syndrome and liver steatosis: increased HDL and reduced body mass index (BMI), waist circumference, triglycerides, liver enzymes, total and low-density lipoprotein (LDL), and CRP. Reductions in BMI, waist circumference, and LDL and increases in HDL became apparent after 6 months of treatment, and these improvements continued over time. Serum cholesterol and triglyceride levels progressively and significantly declined over the first 9 to 12 months and then stabilized. CRP continuously declined, whereas AST declined over the first 12 months, and ALT declined over the first 18 months.

Low testosterone is known to be associated with an increase in fasting insulin and a decrease in insulin sensitivity. A prior pilot study had demonstrated that testosterone therapy has beneficial effects in men with type 2 diabetes. In an oral session chaired by L. S. Chow (University of Minnesota Medical School, Minneapolis), T. H. Jones presented results of the international Testosterone Replacement in Hypogonadal Men With Either Metabolic Syndrome or Type 2 Diabetes (TIMES 2) study—the first large, placebo-controlled, long-term (12-month) study of the effect of exogenous testosterone therapy on insulin resistance and cardiovascular risk factors in hypogonadal men with metabolic syndrome and/or type 2 diabetes.<sup>54</sup> Hypogonadism was defined as TT <11 nmol/L plus ≥2 symptoms. Of the 220 subjects randomly assigned to treatment, 46% completed the 12-month

study (n=95); of these men, 80% had metabolic syndrome, 62% had type 2 diabetes, and 42% had both. Subjects were 37 to 88 years of age (mean, 60±0.62 y) with a mean BMI of 32. Many were taking statins. Daily treatment with 3 g metered-dose 2% testosterone gel (Tostran® 60 mg; ProStrakan Ltd, Galashiels, Scotland) significantly improved many parameters of metabolic syndrome and type 2 diabetes:

- Homeostasis model assessment–insulin resistance baseline to month 12 ratio: 0.836 (95% CI, 0.735, 0.950; *P*=.006)
- By month 12, body fat had decreased about 2% (*P*=.024); decreases in waist circumference reached statistical significance only in patients with type 2 diabetes (*P*=.018)
- Lipoprotein A decreased at each visit and at month 12 was –0.026 g/L below baseline
- A1C decreased significantly in men with type 2 diabetes

Total cholesterol decreased significantly by 6 months, after which dosage adjustments were allowed and significance was lost. Normalization of testosterone levels significantly improved sexual function as measured by the International Index of Erectile Function (IIEF) score in several domains but was most effective for libido. No major testosterone-associated adverse events occurred; PSA increased, but only slightly, in 5 patients. The investigators concluded that the beneficial effects of testosterone therapy on insulin resistance, body composition, glycemic control, and serum lipids could potentially improve overall cardiovascular risk in this population.

### **Ischemic Heart Disease**

Previously, Malkin et al showed that 1 month of intramuscular testosterone therapy (Sustanon® 100, Organon Laboratories Ltd, Cambridge, UK) improved time to exercise-induced myocardial ischemia in 10 hypogonadal men with ischemic heart disease.<sup>55</sup> In an expanded 12-month randomized, placebo-controlled study with long-acting intramuscular TU 1000 mg, treatment of 13 men (baseline TT <12 nmol/L) with chronic stable angina significantly increased the time to exercise-induced cardiac ischemia from 12 seconds to 129 seconds ( $P=.02$ ) as measured by time to 1-mm S-T depression.<sup>56</sup> The improvement was maintained throughout the 12-month study. BMI and triglyceride levels decreased significantly ( $P=.04$  and  $P=.05$ , respectively). Carotid intima thickness decreased, but the difference was not statistically significant. Total cholesterol, HDL, PSA, and mood/symptom scores did not change significantly; hemoglobin increased but remained within the normal range.

### **Virilization for Female-to-Male Transsexuals**

Most previous studies of testosterone in female-to-male transsexuals have been short-term ( $\leq 1$  y).<sup>57-59</sup> In a study from the Netherlands, 17 female-to-male transsexuals were given long-acting intramuscular TU 1000 mg for at least 36 months.<sup>60</sup> After 1 year, dose adjustments were necessary, with the dosing interval shortened to 11 weeks for 6 subjects and lengthened to

13 weeks for 3 subjects. After dose adjustments, serum testosterone levels remained within the normal range for the eugonadal men. Hematocrit increased but did not exceed the normal range after dose adjustments, and no changes occurred in hemoglobin, total cholesterol, or triglyceride values. LDL values decreased slightly, but HDL values did not decrease, which is unusual for women, possibly because of increased muscle mass (weight gain,  $3.5 \pm 1.3$  kg). Thus, intramuscular TU 1000 mg given every 12 weeks over a period of at least 36 months was safe, effective, and convenient for long-term administration to induce and maintain virilization in female-to-male transsexuals.

### **Current Dosing Recommendations May Be Inadequate for Many Men**

A poster presented at both ENDO 2009 and the collateral Endocrine Nurses Society Symposium described results of a study to assess the safety and efficacy of exogenous testosterone therapy in 45 hypogonadal men aged 20 to 75 years (mean, 48 y) using two testosterone formulations: gel 50 mg/d ( $n=8$ ) or long-acting intramuscular TU 1000 mg at weeks 0, 6, 18, and 30 ( $n=37$ ).<sup>61</sup> Safety and efficacy assessments were made at baseline, 3 months, and 12 months for patients using the gel and at baseline and before the second, third, and fourth injections for patients given intramuscular TU. A substantial number of men were undertreated using the recommended dosages. The investigators concluded that, although hematologic and prostatic complications are rare, regular monitoring is critical to ensure timely intervention, and consideration should be given to increasing the doses to achieve satisfactory efficacy in all patients.

# Safety of Exogenous Testosterone Administration for Treatment of Hypogonadism

The safety of long-acting intramuscular TU 1000 mg over 24 to 30 months of therapy was evaluated in a study of 122 men aged 36 to 69 years (mean, 59.5 y) from a private urology practice in Bremerhaven, Germany, and Bayer Schering Pharma.<sup>62</sup> From a baseline of 5.9 to 12.1 nmol/L, testosterone serum concentrations rose over 9 months and stabilized at 18.7 nmol/L while remaining within normal ranges throughout treatment. International Prostate Symptom Scores decreased significantly over 17 months. PSA and prostate volume fluctuated over 12 to 15 months; prostate volume stabilized at pretreatment levels, and PSA stabilized 7.6% ( $2.2 \pm 1.8$  ng/mL) higher than baseline. Statistically significant but not clinically relevant increases in hemoglobin and hematocrit were noted. Larger studies of longer duration are needed, but the results of this small study suggest that long-term administration of testosterone therapy is safe and well tolerated.

Although testosterone therapy has been shown to be safe and well tolerated, concerns remain about its use in men with CVD. A study from the United Kingdom retrospectively analyzed the effect of testosterone therapy in 182 hypogonadal men (mean age, 58.3 y) with type 2 diabetes (53%) and CVD (52%).<sup>63</sup> Hypertension was present in 37%, and 18.6% had had a prior

cardiovascular event. Mean follow-up was 32 months (range, 1 to 114 mo). The mean baseline TT concentration was 7.34 nmol/L. In this population, testosterone therapy was safe. There were no adverse effects on cardiovascular risk factors. After 8 to 13 months of therapy, total cholesterol decreased significantly with no significant change in HDL. Weight, blood pressure, and A1C did not change or improved slightly, and 92% of patients had no change in their diabetes medication. Both PSA and hematocrit increased but stayed within normal ranges. The cardiovascular death rate was lower than expected based on the literature for this population (3.3% vs 13.9%). Two prostate cancers occurred, one after 6 months, suggesting prior undiagnosed disease, and one after 9.5 years of therapy.

Zitzmann and Saad presented overall results of 11 years of experience with intramuscular TU for 183 men (99 primary, 70 secondary, 14 LOH) aged 15 to 70 years (mean, 37 y).<sup>64</sup> Metabolic syndrome was present in 130 men. Testosterone serum trough levels were, in general, in low-normal range. Statistically significant increases in HDL and decreases in LDL, resting blood pressure, waist circumference, and metabolic syndrome were evident by the eighth injection. For all but one patient, in whom prostatitis was later diagnosed, PSA did not exceed 4  $\mu$ g/L. Hematocrit increased significantly but exceeded the normal range on only 13 measurements and never exceeded 54.4%. Dosing intervals for each patient ranged from 10 to 14 weeks. The authors specified that local irritation at the injection site was moderate and transient ( $\leq 3$  d).

# Investigational Products

## Novel Approaches to the Treatment of Male Hypogonadism

In a Friday symposium chaired by Peter J. Snyder, MD (University of Pennsylvania, Philadelphia), John K. Amory, MD (University of Washington Medical Center, Seattle), reviewed recent data on novel therapies in various stages of development: long-acting intramuscular TU 750 mg, novel oral formulations with or without a 5 $\alpha$ RI, and selective androgen-receptor modulators (SARMs).<sup>65</sup>

- The 750-mg dose of long-acting intramuscular TU is effective<sup>66,67</sup> (see details below) and has many advantages, particularly the 10-week dosing interval (Figure 5). This formulation is likely to be available in the United States within the next 6 to 12 months.
- Many men request oral medications. A bioadhesive tablet that adheres to the gums is available in the United States, but few patients find it acceptable. Methylated oral testosterone products have been associated with hepatotoxicity. The newer formulations of oral testosterone in oil are absorbed by the intestinal lymphatics and bypass hepatic metabolism, but they induce supraphysiologic levels of DHT and must be taken with a high-fat meal.<sup>68-70</sup> Although a pharmacokinetic study of oral TU in a self-emulsifying drug delivery system (SEDDS) formulation showed supraphysiologic levels of DHT and testosterone nadirs below the normal range,<sup>71</sup> trials of this drug are continuing. The addition of a 5 $\alpha$ RI to oral testosterone, TE, or TU in sesame oil has been shown to increase bioavailability and maintain DHT in normal ranges<sup>68,69,72</sup> (see details below). A novel nanomilled oral testosterone without oil has shown promise in combination

with a 5 $\alpha$ RI, its pharmacokinetics are not affected by food, and a dose for future studies has been defined.<sup>70</sup> Development of an oral formulation thus faces numerous challenges, and it will probably be several years before one is available in the United States.

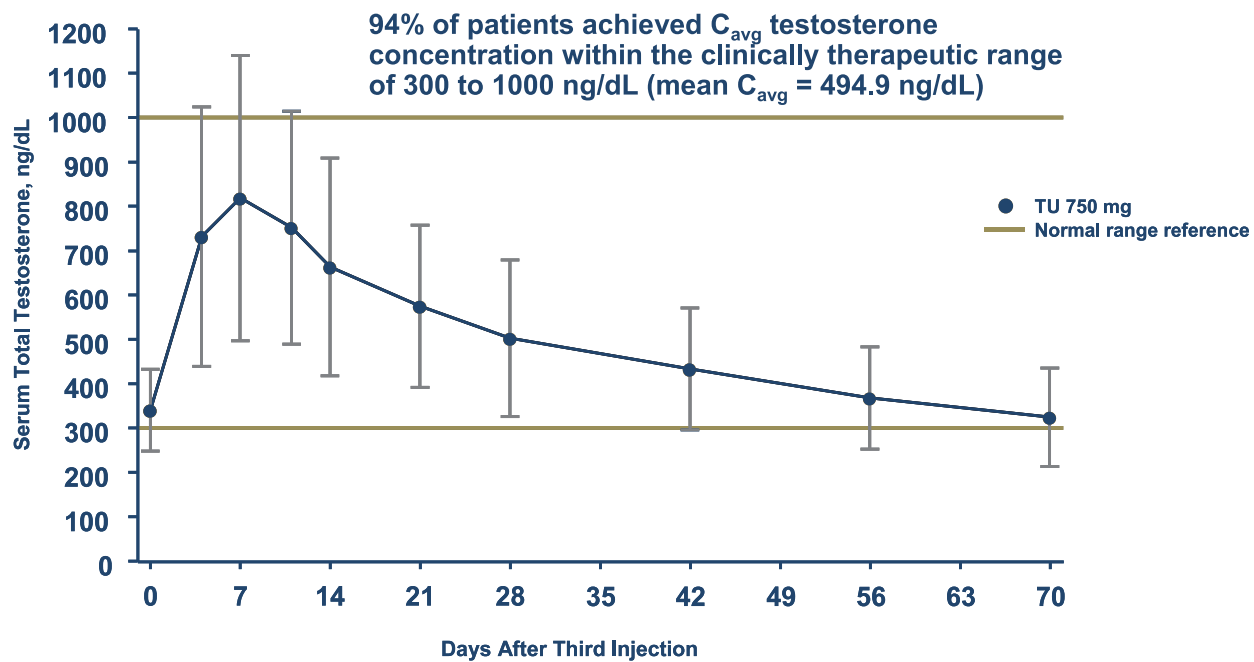
- Another exciting area is the development of SARMs. SARMs lack the androgenic side effects of testosterone and have the potential for once-daily dosing.<sup>73-76</sup> SARMs are currently in early clinical trials for sarcopenia, cancer-related cachexia, osteoporosis, and age-related functional decline, and many others are in various phases of preclinical development.<sup>77</sup> Liver inflammation and increased prostate volume have been problems. SARMs have many potential advantages but also face numerous challenges and are unlikely to be available for treatment of hypogonadism in the foreseeable future.

Many trials of new testosterone formulations are currently recruiting or ongoing: <http://ClinicalTrials.gov/ct2/home>.

## Long-Acting Intramuscular Testosterone Undecanoate

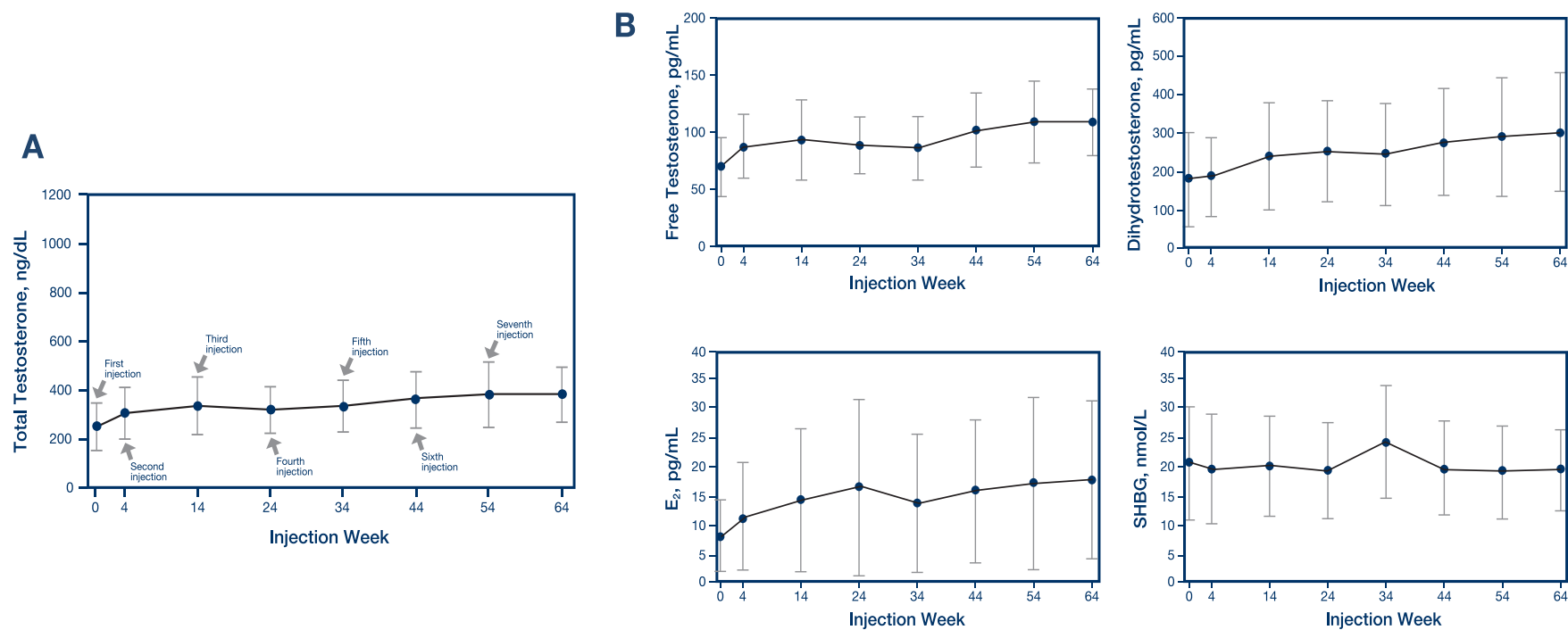
The efficacy and safety of long-acting intramuscular TU 1000 mg has been demonstrated in more than 80 countries worldwide, but it is not available in the United States.<sup>66,78</sup> As noted above, a 750-mg dose is currently under review by the US Food and Drug Administration and is expected to be approved within 6 to 12 months. Wang et al reported the effects of long-acting intramuscular TU 750 mg (Endo Pharmaceuticals Inc., Chadds Ford, PA) on serum TT and other sex hormones in a phase 3 trial.<sup>67</sup> Data were available for 77 men through 64 weeks of treatment (8 injections). Subjects were 18 years of age or older with serum testosterone <300 ng/dL and a mean BMI of 32.4. Serum testosterone reached eugonadal levels after the first injection and remained in the normal range throughout treatment (Figure 6). After achieving steady state, FT, SHBG, DHT, and E<sub>2</sub> remained relatively steady for 64 weeks.

Figure 5. Pharmacokinetics of Intramuscular TU 750 mg Administered With a 10-Week Dosing Interval<sup>66</sup>



$C_{avg}$ , average concentration; TU, testosterone undecanoate.  
Reproduced with permission.

Figure 6. Effect of Intramuscular TU on Mean (SD) Testosterone (A), FT, and Other Sex Hormones (B) at Steady State<sup>67</sup>



E<sub>2</sub>, estradiol; FT, free testosterone; SHBG, sex hormone-binding globulin; TU, testosterone undecanoate.

Reproduced with permission.

### Evaluation of Novel Oral Testosterone Preparations

Results of several pharmacokinetic studies of oral testosterone formulations presented at ENDO 2009 suggest that improved formulations or oral testosterone in combination with a 5 $\alpha$ RI might increase serum testosterone levels.

Htun et al evaluated the pharmacokinetics of a new oral SEDDS formulation of TU (Clarus Therapeutics, Northbrook, IL) in men aged 18 to 65 years with baseline serum testosterone concentrations <250 ng/dL.<sup>71</sup> Twelve men received 100 or 200 mg BID for 1 day; 29 men received 200 or 300 mg BID for 7 days. The 200-mg, 7-day doses were evaluated in the fed or fasting states; the 300-mg doses were given only with food. Based on results of this trial (Table 2), the optimal dose for future trials will be 200 mg with food. The DHT:testosterone ratio rose 2.5-fold with both doses.

**Table 2. Pharmacokinetics of Serum Testosterone Over 12 Hours After Novel Formulation of Oral Testosterone Undecanoate<sup>71</sup>**

	Single Day	7 Days		
	TU 200 mg BID	TU 200 mg BID		TU 300 mg BID
		Fed	Fasting	Fed
n	12 <sup>a</sup>	26 <sup>b</sup>	24 <sup>b</sup>	29 <sup>b</sup>
Cavg 0-12 h, nmol/L	12.1±1.2	18.0±1.6	8.4±0.8 <sup>c</sup>	26.5±2.2
Cmaz 0-12 h, nmol/L	21.7±2.68	33.1±2.88	13.7±1.2	48.9±5.1 <sup>c</sup>
Tmax 0-12 h, min	280±47.4	302±36.6	170±21.0	270±23.4
Number with Cavg within the defined adult male range <sup>d</sup>	9	20	6	25

<sup>a</sup>N=12.

<sup>b</sup>N=29.

<sup>c</sup>Outside the normal range.

<sup>d</sup>10.4-34.7 nmol/L.

Adapted with permission.

The pharmacokinetics of two novel extended-release formulations of external-matrix (EM) oral testosterone (GlaxoSmithKline, Research Triangle Park, NC) were evaluated in 8 healthy men with experimentally induced hypogonadism.<sup>79</sup> Men were given 300-mg doses of immediate release (control), EM slow-release, or EM fast-release oral testosterone. Serum testosterone, DHT, and E<sub>2</sub> all increased significantly into the normal range with all 3 formulations. The EM formulation delayed the time to maximum concentration compared with the immediate-release control formulation. Adverse events were headache (4), hot flushes (2), transient increase in libido (1), and moodiness (1); none was serious. No changes in liver function test results, hematocrit, or creatinine were observed.

Based on results of previous studies,<sup>68,69</sup> a 28-day, open-label phase 2 study was conducted to evaluate the pharmacokinetics of oral testosterone in oil (GlaxoSmithKline, Research Triangle Park, NC) given BID with or without the 5 $\alpha$ RI dutasteride.<sup>72</sup> The 33 subjects, of whom 9 had primary and 24 had secondary hypogonadism, had baseline testosterone concentrations <263 ng/dL. The men received 150, 250, or 400 mg oral testosterone with or without 0.25 mg dutasteride, 400 mg testosterone alone, or 0.25 mg dutasteride alone. Mean 24-hour testosterone concentrations were above 300 ng/dL in 100% of the men who received 400 mg plus dutasteride and in 75% of the men who received 250 mg

plus dutasteride, compared with 50% of those who received 400 mg oral testosterone alone and 29% of those who received oral dutasteride alone. DHT levels decreased in the men who received the combination but increased as expected in those who received testosterone alone. The authors concluded that the combination of oral testosterone and dutasteride provided better bioavailability of testosterone with low rather than elevated levels of DHT compared to testosterone alone.

#### **Pharmacodynamic Dose-Escalating Study With a New Testosterone-in-Matrix Patch**

Raynaud et al reported results of an open-label, placebo-controlled, pharmacodynamic dose-escalation study to determine the dose of testosterone-in-matrix patches (Laboratoires Pierre Fabre, Ramonville, France) that would decrease endogenous testosterone through inhibition of pituitary LH secretion.<sup>80</sup> Subjects (N=39) had serum testosterone concentrations from 200 to 600 mg/dL, and all were symptomatic. Two matrix patches were applied in the morning every other day at doses of 1.2, 1.8, 2.4, 3.0, 3.6, 4.2, and 4.8 mg/d for 8 consecutive periods of 14 days each. Inhibition of LH was dose-dependent. Pituitary inhibition was apparent with the lowest doses, but serum testosterone increased only at the higher doses. DHT increased dose-dependently from 43 $\pm$ 20 ng/dL at baseline to 91 $\pm$ 37 ng/dL at the highest dose. Mean PSA levels increased from 1.4 ng/mL to 2.2 ng/mL. A clear improvement in symptoms was noted at low doses (1.8 to 2.4 mg/d) that increased serum testosterone levels only slightly. The authors concluded that serum testosterone may not be the optimal measure to monitor testosterone supplementation and determine dose adjustment.

## Preclinical Studies—Testosterone: Mechanism of Action

Although some studies report that exogenous testosterone increases muscle mass and strength in older men, findings are inconsistent and the mechanisms are not well understood. Previous studies suggest that testosterone-induced muscle growth in aging mice involves activation of p38 mitogen-activated protein kinase (MAPK)-mediated Notch signaling and/or suppression of c-Jun NH(2)-terminal kinase (JNK) activation.<sup>81</sup> The aim of this study by Kovacheva et al was to investigate the role of testosterone in preventing muscle loss in aging mice and to elucidate signal transduction pathways.<sup>82</sup> Groups of 15 older mice (22 mo old) received a GnRH antagonist followed by implantation of empty (placebo) or testosterone-filled pellets (0.5 or 1.0 cm). Old (24 mo) and young (4 mo) mice were used as controls. The higher doses of testosterone (pellets 1 cm in size) completely prevented age-related decreases in gastrocnemius muscle weight and in the cross-sectional area of fast and slow muscle fibers; suppressed oxidative stress and elevated statin levels, thus preventing JNK activation in skeletal muscles; and prevented age-related decreases in levels of glucose-6-phosphate dehydrogenase (G6PDH), which is an intermediate of glucose metabolism in skeletal muscles. The authors speculated that JNK signaling plays an important role in testosterone-mediated, age-related loss of skeletal muscle mass and that exogenous testosterone promotes muscle growth by inhibiting JNK-mediated apoptosis as well as by stimulating proliferation and augmenting metabolism of muscle cells.

Men with hypogonadism have accelerated atherosclerosis.<sup>83-85</sup> Exogenous testosterone therapy has been reported to decrease symptoms of angina and exercise-induced myocardial ischemia,<sup>55,56,86</sup> but the mechanism of testosterone's action on cardiac arteries is unclear. A study conducted in 32 Polish men (mean age, 63 y) with average endogenous testosterone levels <2.29 ng/mL aimed to determine whether testosterone plays a role in vasodilatation of cardiac arteries via disruption in the prostacyclin-thromboxane (PGI<sub>2</sub>/TXA<sub>2</sub>) balance.<sup>87</sup> Prostacyclin, a vasodilator, and thromboxane, a vasoconstrictor, work together to maintain blood pressure. TE 200 mg was given every 2 weeks for 12 months. Testosterone levels increased significantly from baseline and in comparison with those of 12 untreated control subjects. Results showed a transient increase in urinary excretion of prostacyclin metabolite 6-keto PGF-1 $\alpha$  but no change in the excretion of thromboxane metabolite TXB<sub>2</sub>.

# New Endocrine Society Clinical Practice Guidelines

## Endocrine Treatment of Transsexual Persons

In this well-attended symposium, members of the guidelines committee explained the new guidelines for treatment of transsexual men and women. Briefly, *sex* is physical; *gender identity* is psychological. Gender identity is usually established in early childhood, often as early as 2 or 3 years old. The best time to start treatment is at the beginning of puberty; a GnRH agonist is used to suppress puberty for 1 to 2 years. This strategy allows girls to continue growing and prevents pubertal growth in boys. Unfortunately, no medication is currently approved for this purpose. Treatment and surgery are considered cosmetic and are generally not reimbursed by insurance. Female-to-male transsexuals will need lifelong testosterone therapy. Estrogen

for male-to-female transsexuals has a high risk of adverse outcomes. Family and personal cardiovascular history are important. Virilization or feminization takes 2 to 3 years and cannot be rushed by overdosing. Hormones should not be overdosed; serum levels should be maintained within the normal levels for the cross-sex population. All transsexual persons should be monitored appropriately and regularly while undergoing treatment. An appropriate candidate for endocrine treatment of transsexualism should have a counselor, a general healthcare provider, and an endocrinologist and should have spent 2 years in public as the cross-sex. The final draft of these guidelines had not yet been posted on the Endocrine Society website as of June 30, 2009, but the first draft can be viewed at [http://www.endo-society.org/\\_MDDocReviewFiles/Transgender%20Guideline%20\(1st%20Draft%2011.17.08\).pdf](http://www.endo-society.org/_MDDocReviewFiles/Transgender%20Guideline%20(1st%20Draft%2011.17.08).pdf).

# References

1. Bhasin S, Cunningham GR, Haynes 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. *Endocr Pract.* 2002;8(6):439-456.
3. 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.
4. Tenover JL. Male hormone replacement therapy including “andropause.” *Endocrinol Metab Clin North Am.* 1998;27(4):969-987.
5. Araujo AB. Are men losing their gonads [abstract]? Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract S7-2.
6. Gooren LJ, Behre HM, Saad F, Frank A, Schwerdt S. Diagnosing and treating testosterone deficiency in different parts of the world; results from global market research. *Aging Male.* 2007;10(4):173-181.
7. 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(19):2351-2361.
8. Bhasin S, Woodhouse L, Casaburi R, et al. Older men are as responsive as young men to the anabolic effects of graded doses of testosterone on the skeletal muscle. *J Clin Endocrinol Metab.* 2005;90(2):678-688.
9. Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. *J Clin Endocrinol Metab.* 2008;93(1):68-75.
10. Allan CA. Is testosterone good for the male heart [abstract]? Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract S7-3.
11. McLachlan RI. The free testosterone hypothesis: is it liberating [abstract]? Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract S60-1.
12. Coviello AD. Age-related differences in response to testosterone therapy: the influence of metabolic clearance [abstract]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract S60-2.
13. Calof OM, Singh AB, Lee ML, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J Gerontol Ser A Biol Sci Med Sci.* 2005;60A(11):1451-1457.
14. Gray PB, Singh AB, Woodhouse LJ, et al. Dose-dependent effects of testosterone on sexual function, mood, and visuospatial cognition in older men. *J Clin Endocrinol Metab.* 2005;90(7):3838-3846.
15. 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.
16. Coviello AD, Lakshman K, Mazer NA, Bhasin S. Differences in the apparent metabolic clearance rate of testosterone in young and older men with gonadotropin suppression receiving graded doses of testosterone. *J Clin Endocrinol Metab.* 2006;91(11):4669-4675.
17. Finkelstein JS. Toward a physiologic definition of male hypogonadism: how much testosterone does a man really need [abstract]? Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract S60-3.
18. Pallais JC, Morgentaler A, Barry CV, Hahn CW, Finkelstein JS. Dose-response relationship between testosterone and prostate specific antigen in healthy men [abstract]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract OR42-4.
19. Hayes F. Clinical approach to hypogonadotropic hypogonadism. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009.
20. Palmert MR. Management of hypogonadism through puberty. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009.
21. Rochira V. Clinical issues in management of Klinefelter’s syndrome. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009.
22. Swerdloff RS, Wu FC. Diagnosis and treatment of borderline hypogonadism in the aging male. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009.
23. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. *J Clin Endocrinol Metab.* 2001;86(2):724-731.
24. Crowley WF. Broadening spectrum of hypogonadotropic hypogonadism [abstract]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract S23-2.
25. Raivio T, Falardeau J, Dwyer A, et al. Reversal of idiopathic hypogonadotropic hypogonadism. *N Engl J Med* 2007;357(9):863-873.

# References

26. Corona G, Lee D, Forti G, et al. The relationship between general health and late onset hypogonadism with changes in sexual function in older men: results from the European Male Ageing Study (EMAS) [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P1-157.
27. Haidar A, Yassin A, Saad F, Shabsigh R. Effects of androgen deprivation on glycaemic control and on cardiovascular biochemical risk factors in men with advanced prostate cancer with diabetes. *Aging Male*. 2007;10(4):189-196.
28. Yialamas MA, Dwyer AA, Hanley E, Lee H, Pitteloud N, Hayes FJ. Acute sex steroid withdrawal reduces insulin sensitivity in healthy men with idiopathic hypogonadotropic hypogonadism. *J Clin Endocrinol Metab*. 2007;92(11):4254-4259.
29. Pitteloud N, Mootha VK, Dwyer AA, et al. Relationship between testosterone levels, insulin sensitivity, and mitochondrial function in men. *Diabetes Care*. 2005;28(7):1636-1642.
30. Abate N, Haffner SM, Garg A, Peshock RM, Grundy SM. Sex steroid hormones, upper body obesity, and insulin resistance. *J Clin Endocrinol Metab*. 2002;87(10):4522-4527.
31. Frederiksen L, Hojlund K, Hougaard D, Nielsen TL, Brixen K, Andersen M. No association between insulin sensitivity (euglycemic hyperinsulinemic clamp method) and testosterone after adjustment for central fat mass in men with late onset hypogonadism [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P1-158.
32. Kupelian V, Page ST, Araujo AB, Travison TG, Bremner WJ, McKinlay JB. Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the metabolic syndrome in nonobese men. *J Clin Endocrinol Metab*. 2006;91(3):843-850.
33. Laaksonen DE, Niskanen L, Punnonen K, et al. Testosterone and sex-hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care*. 2004;27(5):1036-1041.
34. Svartberg J. Epidemiology: testosterone and the metabolic syndrome. *Int J Impot Res*. 2007;19(12):124-128.
35. Kara E, Celik O, Kadioglu A, Kadioglu P. Testosterone metabolism and hypogonadism in males over 60 with metabolic syndrome [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P3-302.
36. Foo JP, Chen R, Au V, et al. Androgen deficiency relates to higher cardiovascular risk via poor metabolic status in aging Asian men [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P3-319.
37. Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P. Frequent occurrence of hypogonadotropic hypogonadism in type 2. *J Clin Endocrinol Metab*. 2004;89(11):5462-5468.
38. Dandona P, Dhindsa S, Ghanim H, et al. Estradiol concentrations in males with type 2 diabetes and hypogonadotropic hypogonadism [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P3-318.
39. Haddad RM, Kennedy CC, Caples SM, et al. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc*. 2007;82(1):29-39.
40. 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.
41. Malkin CJ, Pugh PJ, Morris PD, Channer KS, Jones TH. Low bioavailable and total testosterone increases risk of all-cause and cardiovascular mortality in men with proven coronary heart disease—a six year follow up study [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P3-309.
42. Vikan T, Schirmer H, Njolstad I, Svartberg J. Endogenous sex hormones and the prospective associations with cardiovascular disease and mortality in men: the Tromso study [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P3-315.
43. Callou EQ, de Sa FCF, de Oliveira KC, Feres F, Verreschi ITN. Estradiol but not testosterone is related to coronary artery disease in men [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P3-316.
44. Deniz F, Kepez A, Azal O, Kutlu M. Evaluation of vascular reactivity of young hypogonadotropic hypogonadism patients [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P3-320.
45. Schroeder ET, Yarasheski KE, Castaneda-Sceppa C, et al. Eight week change in muscle mass and strength with testosterone and growth hormone administration in older men: the HORMA trial [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P1-153.

# References

46. Kalinchenko SY, Tishova YA, Mskhalaya GZ, Saad F. Can testosterone therapy be included into diabetes treatment in men with metabolic syndrome and hypogonadism [poster]? Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P1-450.
47. 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.
48. Targher G, Chonchol M, Miele L, Zoppini G, Pichiri I, Muggeo M. Nonalcoholic fatty liver disease as a contributor to hypercoagulation and thrombophilia in the metabolic syndrome. *Semin Thromb Hemost*. 2009;35(3):277-287.
49. Targher G. Non-alcoholic fatty liver disease, the metabolic syndrome and the risk of cardiovascular disease: the plot thickens. *Diabet Med*. 2007;24(1):1-6.
50. Marchesini G, Brizi M, Bianchi G, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes*. 2001;50(8):1844-1850.
51. Almeda-Valdés P, Cuevas-Ramos D, Aguilar-Salinas CA. Metabolic syndrome and non-alcoholic fatty liver disease. *Ann Hepatol*. 2009;8(suppl 1):S18-S24.
52. Haider A, Gooren LJ, Padungtod P, Saad F. Improvement of the metabolic syndrome and of non-alcoholic liver steatosis upon treatment of hypogonadal elderly men with parenteral testosterone undecanoate. *Exp Clin Endocrinol Diabetes*. 2009 May 26 [Epub ahead of print].
53. Saad F, Haider A. Testosterone administration to elderly hypogonadal men improves the metabolic syndrome, C-reactive protein and liver steatosis [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P3-308.
54. Jones TH, Channer KS. An international controlled study on the effect of testosterone replacement on insulin resistance in hypogonadal men with metabolic syndrome and/or type II diabetes [abstract]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract OR41-4.
55. Malkin CJ, Pugh PJ, Morris PD, et al. Testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life. *Heart*. 2004;90(8):871-876.
56. Malkin CJ, Mathur A, Channer KS, Jones TH. Testosterone undecanoate therapy improves exercise induced cardiac ischaemia in men with chronic stable angina—a 12 month trial [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P3-306.
57. Jacobeit JW, Gooren LJ, Schulte HM. Long-acting intramuscular testosterone undecanoate for treatment of female-to-male transgender individuals. *J Sex Med*. 2007;4(5):1479-1484.
58. Spinder T, Spijkstra JJ, van den Tweel JG, et al. The effects of long term testosterone administration on pulsatile luteinizing hormone secretion and on ovarian histology in eugonadal female to male transsexual subjects. *J Clin Endocrinol Metab*. 1989;69(1):151-157.
59. Meriggiola MC, Armillotta F, Costantino A, et al. Effects of testosterone undecanoate administered alone or in combination with letrozole or dutasteride in female to male transsexuals. *J Sex Med*. 2008;5(10):2442-2453.
60. Jacobeit JW, Epe M, Schulte HM, Gooren LJ. A three-year safety study of treatment of female-to-male transsexuals with long-acting parenteral testosterone undecanoate [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P2-359.
61. Smith RH, Karavitaki N, Wass JAH. Testosterone replacement in practice—are we giving enough [poster]? Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract NP-3.
62. Saad F, Haider A. Safety study of long-acting parenteral testosterone over 24-30 months [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P2-360.
63. Muraleedharan V, Dugdale CA, Stanworth RD, Jones TH. Testosterone replacement therapy (TRT) in hypogonadal men with cardiovascular disease and/or type 2 diabetes mellitus—a safety audit [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P3-305.
64. Zitzmann M, Saad F. Intramuscular testosterone undecanoate for substitution in male hypogonadism—an experience of 11 years elucidating beneficial effects on cardiovascular risk factors and simultaneously providing a marked degree of safety [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P3-307.
65. Amory JK. Novel approaches to the treatment of hypogonadal men [abstract]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract S49-2.
66. 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):2307-2713.

# References

67. 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 III clinical trial [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P2-358.
68. Amory JK, Bremner WJ. Oral testosterone in oil plus dutasteride in men: a pharmacokinetic study. *J Clin Endocrinol Metab.* 2005;90(5):2610-2617.
69. Amory JK, Page ST, Bremner WJ. Oral testosterone in oil: pharmacokinetic effects of 5 $\alpha$  reduction by finasteride or dutasteride and food intake in men. *J Androl.* 2006;27(1):72-78.
70. Page ST, Bremner WJ, Clark RV, et al. Nanomilled oral testosterone plus dutasteride effectively normalizes serum testosterone in normal men with induced hypogonadism. *J Andrology.* 2008;29(2):222-227.
71. Htun M, Swerdloff R, Entezari A, et al. Pharmacokinetics (PK) of a new formulation of oral testosterone undecanoate (TU) in hypogonadal men [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P2-357.
72. Clark RV, Amory JK, Bush MA, et al. Oral testosterone pharmacokinetics when administered with the 5 $\alpha$ -reductase inhibitor, dutasteride, to hypogonadal men in a 28 day study [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P2-355.
73. Rosen J, Negro-Vilar A. Novel, non-steroidal, selective androgen receptor modulators (SARMs) with anabolic activity in bone and muscle and improved safety profile. *J Musculoskel Neuron Interact.* 2002;2(3):222-224.
74. Gao W, Dalton JT. Ockham's Razor and selective androgen receptor modulators (SARMs): are we overlooking the role of 5 $\alpha$ -reductase? *Mol Interventions.* 2007;7(1):10-13.
75. Morton RA, Barnette KG, Hancock ML, Rodriguez D, Dalton JT, Steiner MS. The use of a selective androgen receptor modulator to improve lean body mass and muscle performance in patients with cancer cachexia [abstract]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract S21-1.
76. Stoch SA, Friedman EJ, Zhou Y, et al. A 12-week pharmacokinetic (PK) and pharmacodynamic (PD) study of MK-0773 in healthy older men [abstract]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract S21-4.
77. Narayanan R, Mohler ML, Bohl CE, Miller DD, Dalton JT. Selective androgen receptor modulators in preclinical and clinical development. *Nuc Rec Signaling.* 2008;6:e010.
78. Von Eckardstein S, Nieschlag E. Treatment of male hypogonadism with testosterone undecanoate injected at extended intervals of 12 weeks: a phase II study. *J Androl.* 2002;23(3):419-425.
79. Snyder CN, Caricofe RB, Clark RV, Bush MA, Bremner WJ, Amory JK. Pharmacokinetics of two novel formulations of external matrix oral testosterone in normal men with experimental hypogonadism [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P2-354.
80. Raynaud JP, Garrigue E, Hucher M, Gardette J. Effect of escalating doses of testosterone on LH levels in low testosterone eugonadal male volunteers [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P2-356.
81. Brown D, Hikim AP, Kovacheva EL, Sinha-Hikim I. Mouse model of testosterone-induced muscle fiber hypertrophy: involvement of p38 mitogen-activated protein kinase-mediated Notch signaling. *J Endocrinol.* 2009;201(1):129-139.
82. Kovacheva EL, Shen R, Assanah E, Sinha-Hikim I. Testosterone supplementation through inhibition of oxidative stress and JNK-signalling and stimulation of cellular metabolism prevents age-related loss of skeletal muscle mass [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P1-154.
83. Alexandersen P, Haarbo J, Byrjalsen I, Lawaetz H, Christiansen C. Natural androgens inhibit male atherosclerosis: a study in castrated, cholesterol-fed rabbits. *Circ Res.* 1999;84:813-819.
84. English KM, Mandour O, Steeds RP, Diver MJ, Jones TH, Channer KS. Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. *Eur Heart J.* 2000;21(11):890-894.
85. Hougaku H, Fleg JL, Najjar SS, et al. Relationship between androgenic hormones and arterial stiffness, based on longitudinal hormone measurements. *Am J Physiol Endocrinol Metab.* 2006;290(2):E234-E242.
86. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina. *Circulation.* 2000; 102(16):1906-1911.
87. Rabijewski M, Papierska L, Zgliczynski W. The influence of testosterone enanthate on urine excretion of prostacyclin and thromboxane metabolites in men with testosterone deficiency syndrome [poster]. Presented at: Endocrine Society annual meeting; Washington, DC; June 10-13, 2009. Abstract P2-352.

**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)