# Experts Debate When to Treat Androgen Deficiency

BY MARY ELLEN SCHNEIDER
*New York Bureau*

BOSTON — Testosterone therapy should not be offered to all older men with low testosterone levels, according to experts commissioned by the Endocrine Society to examine the treatment of androgen deficiency in adult men.

Guidelines issued by the task force members advise that physicians instead offer testosterone therapy on an individual basis to older men with consistently low testosterone levels on more than one occasion and clinically significant symptoms of androgen deficiency. The guidelines were published in June (J. Clin. Endocrinol. Metab. 2006;91:1995-2010).

But task force members disagreed about the serum testosterone threshold that should trigger therapy in older men with symptoms of androgen deficiency, Dr. Shalender Bhasin, chair of the task force, said at the annual meeting of the Endocrine Society. Some would initiate treatment in symptomatic older men with testosterone levels less than 300 ng/dL; others favored a threshold of 200 ng/dL, saying the severity of symptoms should guide treatment.

The Endocrine Society decided to address the treatment of androgen deficiency because it's an area with rapid advances in basic science and product development. In addition, testosterone prescriptions are up; but at the same time, there is considerable misinformation and controversy surrounding the use of testosterone therapy, said Dr. Bhasin, who is chief of endocrinology at Boston University.

"We tried to do the right thing," he said. "We anguished a great deal because of the realization that … we know so little."

The new guidelines are based on systematic reviews of available evidence and discussions among the task force members. They outline recommendations for diagnosis, screening, treatment, and monitoring for testosterone therapy in adult men with androgen deficiency syndromes.

## Diagnosis

The members of the task force opposed screening for androgen deficiency in the general population because of a lack of consensus on the case definition and a lack of data on the public health impact of androgen deficiency.

The experts recommended making the diagnosis of androgen deficiency only in individuals with consistent symptoms and signs of low serum testosterone levels. A diagnosis should not be made during an acute or subacute illness, Dr. Bhasin said.

The diagnosis can be challenging because the signs and symptoms of androgen deficiency are nonspecific and appropriate threshold testosterone levels are unknown and may depend on age, Dr. Bhasin said. Further, testosterone measures may vary because of circadian rhythms as well as accuracy problems with commercial assays, he said.

The task force advised using a reliable assay to measure the morning total testosterone level to establish the diagnosis and confirming it either by repeating the measurement of morning total testosterone or by measuring the free or bioavailable testosterone level.

## Treatment

Testosterone therapy is appropriate in symptomatic men who have classic androgen deficiency syndromes and low testosterone levels, according to the guidelines. The therapy should be used to induce and maintain secondary sex characteristics. It can also be used to improve sexual function, sense of well-being, muscle mass, strength, and bone mineral density.

Testosterone therapy is not appropriate in patients who have metastatic prostate cancer, breast cancer, or a palpable prostate nodule or induration. Patients with a prostate-specific antigen (PSA) greater than 3 ng/mL without further urological evaluation are not candidates for testosterone therapy. Other contraindications noted in the guidelines include erythrocytosis, hyperviscosity, untreated obstructive sleep apnea, severe benign prostatic hyperplasia symptoms, or uncontrolled severe heart failure.

Because of a lack of randomized controlled trial data, the task force did not make a recommendation on the treatment of men with prostate cancer who have been disease free for two years or more.

For HIV-infected men who have low testosterone levels and weight loss, the task force members suggested short-term testosterone therapy as an adjunctive approach to promote weight maintenance and improvements in lean body mass and muscle strength.

## Monitoring

The task force recommended a standardized monitoring plan with evaluation and measures of testosterone levels at 3 months after initiating treatment and annual assessments.

Hematocrit should be measured at baseline, 3 months, and annually, the task force recommended. If hematocrit exceeds 54%, therapy should be stopped until hematocrit decreases to a safe level. Therapy can be restarted at a lower dose, but evaluations for hypoxia and sleep apnea should be conducted, the task force recommended.

The task force recommended urological consultation if there is a verified serum or plasma PSA concentration of more than 4.0 ng/mL or an increase in serum or PSA concentration of more than 1.4 ng/mL in any 12-month period. ■

# Low Level of Testosterone May Increase All-Cause Mortality Risk

BY MARY ANN MOON
*Contributing Writer*

Men with low testosterone levels seem to be at increased risk of death from all causes and to have shorter survival times than men with normal testosterone levels, said Dr. Molly M. Shores of the departments of psychiatry and behavioral sciences at the University of Washington, Seattle, and associates.

In a recent small study, the researchers had found that men with a low testosterone level had higher 6-month mortality than did those with a normal level who were of similar age and had comparable medical morbidity. "Given these unforeseen preliminary findings, we conducted the present retrospective cohort study to examine if repeatedly low serum testosterone levels were associated with increased mortality in a larger sample of middle-aged and elderly men with a longer follow-up, of up to 8 years," they said.

Dr. Shores and her associates identified in a clinical database 858 male veterans, aged 40 years and older, who had undergone at least two measures of testosterone levels between 1994 and 1999 and had then been followed for a mean of 4.3 years. They matched the data on these subjects with data in a national Veterans Affairs death registry to obtain mortality information.

The reasons why these men had undergone testosterone testing were not available for analysis, but previous research has shown that, in general, the most common clinical indications are evaluation of sexual dysfunction, osteoporosis, genitourinary conditions, and endocrine conditions, the investigators said (Arch. Intern. Med. 2006;166:1660-5).

A total of 452 men—53% of the study population—had normal serum testosterone levels (defined as 250 ng/dL or higher), or normal free testosterone levels (defined as 0.75 ng/dL or higher). Another 240 men (28%) had equivocal levels, and 166 (19%) had low levels.

Because testosterone levels decrease with acute and chronic illness, the prevalences of chronic obstructive pulmonary disease, HIV infection, coronary artery disease, and hyperlipidemia were noted. There were no significant differences between the men with normal testosterone levels and those with low testosterone levels regarding these disorders or overall medical morbidity.

All-cause mortality was 20% in men with normal testosterone levels and 25% in those with equivocal levels, compared with 35% in men with low levels. After the data were adjusted to account for the covariates of age, race, body mass index, and other clinical factors, "low testosterone level continued to be associated with an increased mortality risk of 88% greater than in men with normal testosterone levels," the authors wrote.

To control for the confounding influence of possible acute illness, they conducted an analysis excluding all subjects who died within 1 year of having their testosterone levels measured. In this subset of subjects, low testosterone levels were still associated with a 68% greater mortality risk, compared with normal levels.

The findings do not show that low testosterone levels directly raise mortality risk, because "a retrospective cohort study cannot establish a causal relationship." Large, prospective studies would clarify the issue, they wrote. ■

# *Low Testosterone Associated With Prostatic Conditions*

CHICAGO — Men with prostatic disease often present with symptoms of hypogonadism and are more likely to be hypogonadal, compared with patients who do not have prostatic conditions, Dr. Sherwyn L. Schwartz said in a poster presentation at the annual meeting of the American Association of Clinical Endocrinologists.

As part of the Hypogonadism in Males (HIM) study, Dr. Schwartz, an endocrinologist in private practice in San Antonio, looked at 391 men aged 45 or older who had prostatic disease and made appointments at 95 primary care centers over a 2-week period. Patients included 165 men with serum total testosterone levels of less than 300 ng/dL, defined as hypogonadal levels, and 226 men with normal serum total testosterone levels.

All patients had a single morning blood draw to test for concentrations of total testosterone, free testosterone, bioavailable testosterone, and sex hormone–binding globulin. They were surveyed for comorbid conditions and for signs and symptoms of hypogonadism, such as decline in general feeling of well-being, decline in muscular strength, decrease in sexual desire, and depressed mood. Dr. Schwartz compared study results in this group with results from the overall HIM study population.

In the overall study population, the percentage of hypogonadal men with a medical history of prostatic disease or disorder was 20%, similar to the 17% prevalence seen in eugonadal men. But in the hypogonadal population not receiving testosterone therapy, 21% had prostatic disease, which was statistically significant when compared with the prevalence in eugonadal men.

Similarly, the risk for hypogonadism in the overall study population was comparable for men with and without prostatic disease. But for the untreated population, the risk of hypogonadism in men with prostatic disease was significantly greater than in men with no history of prostatic disease. "Larger studies that examine the relationship between the occurrence of hypogonadal symptoms and the risk of hypogonadism in men aged 45 or older with and without prostatic diseases or disorders are warranted," he concluded.

**—Joyce Frieden**