A Clinical Conundrum: The Diagnosis and Treatment of Androgen Deficiency in Older Men

Testosterone replacement in young men with hypogonadism maintains or improves bone mineral density, body composition, virilization, libido, sexual function, and sense of well-being. As men age, however, it is difficult to differentiate true hypogonadism from the changes of normal aging. There is uncertainty if the physiologic changes of aging are due to testosterone deficiency and if treating normal older men with testosterone is beneficial. Because testosterone-dependent diseases such as benign and malignant prostate growth become very common as men age, the risk/benefit ratio for testosterone replacement in older men is more difficult to define than it is in young men.

Large epidemiologic studies document a decline in testosterone production and an increase in sex hormone–binding globulin (SHBG) as men age, resulting in a much greater decline in the active

**Figure.** Total and bioavailable testosterone (T) levels from 346 men in Rochester, Minnesota, stratified by age. (Data from Khosla S, et al: Relationship of serum sex steroid levels and bone turnover markers with bone mineral density in men and women: a key role for bioavailable estrogen. J Clin Endocrinol Metab 1998;83:2266-74. Copyright 1998, The Endocrine Society. Reprinted with permission.)
fraction, measured as free or bioavailable testosterone (Figure). Most studies testing the effects of testosterone administration in normal elderly men included men older than 60 years whose baseline total testosterone levels were in the low-normal to mildly low range (e.g., <350 ng/dL) or had bioavailable testosterone levels less than 70 ng/dL. These studies, most of which were published between 1990 and 2002, have been of short duration and included relatively small numbers of subjects. Although the results from the various studies are not entirely consistent, a composite of the changes seen with testosterone treatment in older men is shown in the Table. Todd B. Nippoldt, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, cautions: “It is important to emphasize that there are no data on clinically important end points, such as bone fracture risk, cardiovascular events, development of malignancy, or mortality, for testosterone treatment in normal elderly men.”

Men with gynecomastia; osteoporosis; diminished libido; erectile dysfunction; loss of muscle mass, beard, or body hair; or hot flashes warrant an evaluation for hypogonadism. Because of the increased level of SHBG with aging, the laboratory evaluation in older men should start with a measurement of total testosterone along with free or bioavailable testosterone. Dr Nippoldt notes: “It is important to determine the etiology of a low testosterone level before starting replacement therapy. Blood levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin should be measured in all men with low testosterone levels. Elevated serum LH and FSH concentrations indicate primary testicular failure, and no further studies are needed. Elevated

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serum prolactin levels, in the absence of prolactin-
increasing drugs, should dictate computed imaging of
the sellar region.”

Low (or “inappropriately normal”) LH and FSH imply
a central cause for hypogonadism, which may be
functional or structural. A functional abnormality in
the hypothalamic-pituitary axis is more common. This
functional abnormality may be idiopathic or due to
“normal aging,” but several medical conditions should
be considered as well: obstructive sleep apnea, recent
illness or surgery (eugonadal sick syndrome), extreme
emotional distress, or adverse effects of medications
(eg, high-dose glucocorticoids, narcotic pain relievers,
or drugs that increase prolactin). The only way to
definitively exclude a structural lesion is by sellar
computed imaging. The decision to obtain sellar MRI
depends on the severity of the deficiency, the patient’s
age, and the potential presence of other pituitary
dysfunction or mass effect (eg, headaches or vision
disturbance).

The decision on whether to begin testosterone
replacement in an elderly man may be difficult.
There are no definitive data regarding the level of
testosterone required to prevent osteopenia and
maintain muscle mass. However, values of total
testosterone <200 ng/dL or bioavailable testosterone
<70 ng/dL are probably inadequate, and patients with
these levels should be considered for replacement,
even in the absence of hypogonadal symptoms.
Many men have symptoms compatible with
hypogonadism with testosterone values at the lower
end of the normal range or just mildly diminished,
and it is difficult to know if this is the cause for these
symptoms. Dr Nippoldt says: “In this situation,
a therapeutic trial of testosterone replacement is
warranted. Replacing testosterone in doses adequate
to bring the total testosterone level to the mid-normal
range and bioavailable testosterone level >80 ng/dL
for at least 3 months is usually an adequate trial.
Elderly men metabolize testosterone at a slower rate
than younger men and usually require lower doses
than those typically used for young hypogonadal men.
If the testosterone replacement trial has no impact on
the symptoms, testosterone replacement should be
discontinued.”

Potential risks for parenteral testosterone replacement
include exacerbating or unmasking benign

prostatic hypertrophy, prostate cancer, obstructive
sleep apnea, and polycythemia. No studies have
defined the incidence of these potential risks or
the cost-effectiveness of pretreatment screening or
monitoring. Dr Nippoldt advises: “In the absence of
these data, it is reasonable to obtain baseline digital
rectal examination, prostate-specific antigen level,
complete blood cell count, and a history regarding the
potential for obstructive sleep apnea. The frequency
of rechecking these studies during therapy depends
on the patient’s age, family history, and baseline
values. Any new symptom should be investigated. If
polycythemia develops, overnight polysomnography
should be considered to exclude obstructive sleep
apnea.”

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A Practical Approach to the Patient With Subclinical Hypothyroidism

Subclinical hypothyroidism occurs when the serum thyroid-stimulating hormone (TSH) level rises above the upper limit of normal (ULN) despite a normal serum free thyroxine (FT4) concentration. Subclinical hypothyroidism or mild thyroid failure is a common problem with a prevalence of 4% to 8.5% in the adult population. The prevalence of subclinical hypothyroidism increases with advancing age and is higher in women (Figure).

Figure. Serum TSH levels in 123,958 patients aged 50 years or older seen at Mayo Clinic, 1995–1997.

Because serum TSH has a log-linear relationship with circulating thyroid hormone levels (eg, a 2-fold change in FT4 produces a 100-fold change in TSH), it is the key test for the diagnosis of subclinical hypothyroidism. Vahab Fatourechi, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, notes: “The laboratory reference ranges for TSH and FT4 may not be representative of a given individual’s personal normal range. That is, the laboratory reference ranges are wider than the ranges of thyroid hormones that are typically observed in an individual over time. For the diagnosis of subclinical hypothyroidism, other causes of elevated serum TSH, such as recovery from nonthyroidal illness, assay variability, heterophil antibodies, central hypothyroidism with biologically inactive TSH, and thyroid hormone resistance, should be excluded. However, the most common cause of elevated serum TSH is autoimmune thyroid disease.”

What Is the Upper Limit of Normal for TSH?
The ULN for serum TSH is the subject of hot debate. The reference range used by Mayo Medical Laboratories is 0.3 to 5.0 mIU/L. However, data that support a move to lower the ULN of TSH to 3.0 mIU/L and possibly 2.5 mIU/L have been published. These lower ULN cutoffs are obtained if individuals at risk of thyroid disease are excluded from the reference range population. The strongest argument for lowering the ULN of TSH is the higher rate of positive antithyroid antibodies (reflecting underlying autoimmune thyroid disease) for individuals with TSH concentrations between 3 and 5 mIU/L and the higher rate of progression to clinical thyroid disease for this subgroup. The argument against lowering the ULN for serum TSH is that 22 million to 28 million additional individuals in the United States would be considered hypothyroid if the ULN of the TSH range were decreased to 2.5 to 3.0 mIU/L. Dr Fatourechi cautions: “Our own data show that decreasing the ULN of the TSH reference range to 3.0 mIU/L results in a 3-fold increase in the diagnosis of hypothyroidism in patients without a history of thyroid disease. Yet there is no evidence that intervention at these levels of TSH is beneficial. In fact, some evidence shows that lowering serum TSH to the proposed new normal range by adjustment of the thyroxine dose does not improve patients’ well-being or their nonspecific complaints.” Dr Fatourechi continues: “Obviously for patients with TSH levels between 3 and 5 mIU/L, follow-up and possibly measurement of thyroperoxidase (TPO) antibody may be considered.”

Should All Patients With Subclinical Hypothyroidism Be Treated With Thyroid Hormone Replacement?
There is consensus for initiating thyroxine replacement therapy for all patients with elevated TSH higher than 10 mIU/L, even if FT4 is within the normal laboratory range. However, controversy continues concerning whether patients with serum TSH levels between 5 and 10 mIU/L should be treated. The argument in favor of replacement therapy is based on numerous proposed consequences of untreated subclinical hypothyroidism: progression to clinical hypothyroidism, subtle systemic symptoms of hypothyroidism, lipid abnormalities, adverse cardiac end points, cardiac dysfunction, adverse fetal effects
and pregnancy outcomes, possible contribution to infertility, neuromuscular dysfunction, psychiatric dysfunction, and cognitive dysfunction.

Dr Fatourechi explains: “If studies show that mildly elevated serum TSH has adverse cardiac effects, then therapy of all cases of subclinical hypothyroidism will make sense. Several investigators have demonstrated subtle cardiovascular dysfunction in subclinical hypothyroidism, but clinical significance is questionable. However, to date, most studies have shown a lack of association of subclinical hypothyroidism with cardiac events and cardiovascular mortality. Surprisingly, the results of an epidemiologic study suggested that for individuals older than 80 years a slightly higher-than-normal TSH had survival benefit. Because of the large number of individuals potentially impacted, there is an urgent need for settling this controversy. Until guidance from carefully designed randomized trials becomes available, individuals with serum TSH levels between 5 and 10 mIU/L should be treated selectively. Thyroxine replacement therapy should be reserved for patients who have goiter, women who are anticipating pregnancy or are pregnant, or patients with depression or bipolar disorder. Patient preference, clinical circumstance, age, presence of symptoms of hypothyroidism, TPO antibody positivity, and level of and progression of TSH over time should also be considered. We also suggest that subclinical hypothyroidism associated with autoimmune thyroiditis of children and adolescents should be treated. Our data show that patients with serum TSH levels above 8 mIU/L have a high likelihood of progression to TSH above 10 mIU/L in 4 years and may be considered for thyroxine replacement therapy.

“Improvement in serum lipid levels with thyroxine replacement therapy is more likely for patients who have baseline TSH levels higher than 10 mIU/L. If hyperlipidemia is encountered in a patient with a serum TSH between 5 and 10 mIU/L, specific lipid-directed therapy or lifestyle changes are needed. Some of these recommendations do not have definitive evidence-based support; however, we believe a practical approach is needed until more evidence becomes available.”

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Focus on Education

Biomarkers of Cardiovascular Risk: State of the Art

October 30-31, 2007
Leighton Auditorium
Harold W. Siebens Medical Education Building
Mayo Clinic, Rochester, Minnesota

This conference will provide an overview of advances in the use of biomarkers in cardiovascular risk stratification in asymptomatic individuals, in particular the use of proteomic markers. Topics will include the assessment of atherosclerotic burden, testing of arterial function, emerging markers, current approaches to cardiovascular risk stratification, statistical approaches to biomarker validation, novel platforms, regulatory issues, and perspectives from industry. For additional information, go to www.mayomedicallaboratories.com/education where you will find a comprehensive list of programs including Biomarkers of Cardiovascular Risk and information on registration.
Process Announcement

New Requirement for Submissions for Surgical Pathology Consultations

Effective October 1, 2007, a pathology report must accompany all specimens submitted for #5439 Surgical Pathology Consultation. If a pathology report is not received with the specimen, the case will not be reviewed or processed and, therefore, significant reporting delays may occur.

The new requirement affects all #5439 Surgical Pathology Consultation cases and Special Procedure cases. The latter include estrogen and progesterone receptor assay/immunoperoxidase stains, Her2/neu immunoperoxidase stain, DNA ploidy, digital image analysis (DIA), EGFR immunoperoxidase stain, as well as HPV, CMV, HSV, EBV, JCV, and varicella-zoster in situ hybridization.

The following information is required when a case (slides or blocks) is submitted for a consultative opinion or special testing:

1. A copy of either your preliminary or final pathology report that includes:
   - Patient name
   - Patient gender
   - Patient age or date of birth
   - Specimen source
   - Your accession/case number (number must match the labeling on the accompanying slides or blocks)
   - Note: Special Procedures cases must also include either your preliminary or final diagnosis; however, this is not required for consultation cases.

   If a pathology report is not received with the slides and/or blocks, the case will not be reviewed or processed. We will call you to request the report via fax.

2. Include #5439 Surgical Pathology Consultation (or the appropriate Special Procedures test number) and your preassigned client number on the request for testing.

3. For orders placed electronically, complete the appropriate section of the Mayo Connect Additional Information Form indicating specimen type sent and submit a copy of your pathology report.

4. For orders submitted manually, complete a Mayo Medical Laboratories Test Request Form.

5. If you submit manually and do not have a Mayo Medical Laboratories Test Request Form, or you do not have a preassigned account number, you must provide the following information on your facility letterhead:
   - Hospital/Institution name
   - Complete mailing address
   - Phone number and fax number
   - Requesting pathologist’s name and direct phone number
   - Test requested (eg, #5439 Surgical Pathology Consultation)
   - Specimen source

For your convenience, our Surgical Pathology kit (Supply T554) is available through Mayo Medical Laboratories for use when submitting a Surgical Pathology Consultation case.

If you have questions regarding these updated requirements, please call Mayo Laboratory Inquiry at 800-533-1710. Additional information is also available online at www.mayomedicallaboratories.com.
Abstracts of Interest

Stratification of Patient Risk Based on Prostate-Specific Antigen Doubling Time After Radical Retropubic Prostatectomy

Matthew K. Tollefson, MD; Jeffrey M. Slezak, MS; Bradley C. Leibovich, MD; Horst Zincke, MD; and Michael L. Blute, MD

OBJECTIVES: To assess the risk of local recurrence, systemic progression, and death from cancer among patients who experience biochemical relapse after radical retropubic prostatectomy and to stratify those patients by prostate-specific antigen (PSA) doubling time (DT).

PATIENTS AND METHODS: We identified patients who experienced biochemical recurrence (defined as a PSA level ≥0.4 ng/mL) after radical prostatectomy from January 1, 1990, to December 31, 1999, for prostate adenocarcinoma. The PSA-DT was calculated by log linear regression using all PSA values within 2 years of biochemical recurrence. Local recurrence- and systemic progression-free survival and cancer-specific survival were estimated using the Kaplan-Meier method and analyzed by the log-rank test and Cox models.

RESULTS: Biochemical recurrence was noted in 151 (7%) of 5533 men during the follow-up period. Of the 1064 patients with a calculable PSA-DT, 322 (30%) had a PSA-DT of less than 1 year, 357 (34%) had a PSA-DT of 1 to 9.9 years, and 385 (36%) had a PSA-DT of 10 years or more. Patients with a PSA-DT of 10 years or more were less likely to have a higher preoperative PSA level, Gleason score, advanced pathologic stage, and seminal vesicle invasion. Patients with a PSA-DT of 10 years or more were at low risk of local recurrence (hazard ratio [HR], 0.09; 95% confidence interval [CI], 0.06–0.1; compared with patients with a PSA-DT of <1 year), systemic progression (HR, 0.05; 95% CI, 0.02–0.13), or death from cancer (HR, 0.15; 95% CI, 0.05–0.43).

CONCLUSIONS: Prostate-specific antigen DT is an independent predictor of clinical disease recurrence and mortality after surgical biochemical failure. Risk stratification into high-, intermediate-, and low-risk categories based on the PSA-DT provides helpful clinical information and assists in the development of salvage therapy trials.

Mayo Clinic Proceedings 2007;82(4):422-427
Upcoming Education Conferences . . .

**Practical Surgical Pathology**
September 13–15, 2007
Mayo Clinic • Rochester, Minnesota

**Quality Phlebotomy: Beyond the Basics**
September 24, 2007
Marriott Washington Dulles Airport • Dulles, Virginia

**State-of-the-Art Thrombophilia: A Practical Clinical Conference**
October 4–5, 2007
The Kahler Grand Hotel • Rochester, Minnesota

**Biomarkers of Cardiovascular Risk: State of the Art**
October 30–31, 2007
Mayo Clinic • Rochester, Minnesota

**Real-Time PCR for the Clinical Microbiology Laboratory**
November 15–16, 2007
Mayo Clinic • Rochester, Minnesota

Disease Management Strategies . . .

**Breast Cancer**
September 20, 2007
Presenter: Matthew P. Goetz, MD

**Oral Anticoagulation Management Update**
October 11, 2007
Presenter: Robert D. McBane, MD

**Overview of Inflammatory Bowel Disease**
November 13, 2007
Presenter: Edward V. Loftus Jr., MD

**Celiac Disease**
December 11, 2007
Presenter: Joseph A. Murray, MD

FOR MORE INFORMATION contact Mayo Medical Laboratories Education Department at 800-533-1710 or visit us at MayoMedicalLaboratories.com/education

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