What is the evaluation and management of hypogonadism in elderly men?

The primary difficulties of diagnosing hypogonadism in elderly men are: 1) the fact that many of the symptoms progress so gradually as to be almost imperceptible and, 2) closely resemble many of the symptoms attributed to aging in general. “The effect of T [testosterone] on the central nervous system extends beyond sexual behavior. T has been shown to alter mood, memory, ability to concentrate, and the overall sense of vigor and well being that may interact with a host of other psychologic changes associated with aging.”

Symptoms and findings of testosterone deficiency are similar to those associated with aging. They include loss of energy, depressed mood, decreased libido, erectile dysfunction, decreased muscle mass and strength, increased fat mass, frailty, osteopenia, and osteoporosis. “Such age-associated T deficiency, which has been termed ‘andropause’, is thought to be responsible for a variety of symptoms experienced by elderly men, such as weakness, fatigue, reduced muscle and bone mass, impaired haematoipoiesis, oligospermia, sexual dysfunction, depression, anxiety, irritability, insomnia and memory impairment.”

After studying recommendations from “An International Consultation in collaboration with the major urology and sexual medicine associations [which] assembled over 200 multidisciplinary experts from 60 countries into 17 committees,” Morales et al. summarize:

Hypogonadism is a clinical and biochemical syndrome characterized by a deficiency in serum androgen levels which may decrease sexual interest, quality of erections and quality of life. Biochemical investigations include testosterone and either bioavailable or calculated free testosterone; prolactin should be considered when hypogonadism has been documented. If clinically indicated, androgen therapy should maintain testosterone within the physiological range avoiding supraphysiologic values. Digital rectal examination and determination of serum prostate specific antigen values are mandatory prior to therapy and regularly thereafter. Androgen therapy is usually long-term requiring regular follow-up, frequent monitoring of blood levels and beneficial and adverse therapeutic responses.

Makshida et al. found a fascinating correlation between hypogonadism and metabolic disease and, in fact, suggest that hypogonadism may be one of metabolic syndrome’s central attributes along with obesity, insulin resistance, hypertension and hyperlipidemia. They conclude:

Hypogonadism is likely a fundamental component of metabolic syndrome. Testosterone therapy may not only treat hypogonadism, but may also have tremendous potential to slow or halt the progression from metabolic syndrome to overt diabetes or cardiovascular disease via beneficial effects on insulin regulation, lipid profile and blood pressure. Furthermore, the use of testosterone to treat metabolic syndrome may also lead to the prevention of urological complications commonly associated with these chronic disease states, such as neurogenic bladder and erectile dysfunction.

Thus, where other authors stress the fact that erectile function may not necessarily reflect hypogonadism so much as vascular, neurologic or psychogenic disease, Makshida et al. take this one step further in suggesting that vascular or neurologic disease—felt to be causing sexual dysfunction—may in fact be simply different manifestations of the same underlying disorder—namely metabolic syndrome—which also causes hypogonadism.

While the authors referenced above are enthusiastic about testosterone replacement, many others caution against overenthusiastic prescribing of testosterone. Hijazi & Cunningham, for example, note that:

Several small clinical trials indicate that testosterone replacement therapy can improve many of these findings; however, the studies have not been powered to assess potential risks, such as the need for invasive treatment of benign prostatic hyperplasia, development of a clinical prostate cancer, or cardiovascular events. Thus, the benefit/risk ratio of testosterone replacement therapy in aging men is not known.

Kaufman and Vermeulen in their 2005 article, “The decline of androgen levels in elderly men and its clinical and therapeutic implications,” note that although (normal) aging men can clinically resemble younger men with hypogonadism, androgen levels in aging males vary widely. Furthermore the significance of these variations in androgen levels has been inadequately studied and is therefore poorly understood.

In fact, minimal androgen requirements for elderly men remain poorly defined and are likely to vary between individuals. Consequently, borderline androgen deficiency cannot be reliably diagnosed in the elderly, and strict differentiation between “substitutive” and “pharmacological” androgen administration is not possible. To date, only a few hundred elderly men have received androgen therapy in the setting of a randomized, controlled study, and many of these men were not androgen deficient. Most consistent effects of treatment have been on body composition, but to date there is no evidence-based documentation of clinical benefits of androgen administration to elderly men with normal or moderately low serum testosterone in terms of diminished morbidity or of improved survival or quality of life.

Screening/ Diagnosis of Hypogonadism

Morales et al. offer a comprehensive summary of diagnostic measures used to diagnose hypogonadism. This includes a summary of clinical features, a discussion of the various screening questionnaires and a discussion of the difficulties inherent in the various serum tests. Some of the latter include:

1. Confounding caused by active metabolites when testosterone is metabolized within tissues.
2. “Interindividual differences in androgen sensitivity.”
3. The natural increase in sex hormone binding globulin (SHBG) with age which translates to a decrease in bioavailable [free and albumin-bound fractions] testosterone.
4. A “flattening of the circadian rhythm leading to steady low levels of androgens throughout the 24 hour cycle.”
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Morales et al. note that free testosterone “provides a more reliable index of androgenicity” 4(p.75) and, although they mention some of the difficulties with particular assays, do state that the ammonium sulphate precipitation method is generally “more commonly accessible, reliable, and less expensive.” 4(p.75) They refer the reader to the Free & Bioavailable Testosterone calculator developed by Vermeulen (http://issam.ch/freetesto.htm) and available from the International Society for the Study of the Aging Male’s website (http://issam.ch).

Morley et al. also discuss the convenience (though not superiority) of measuring salivary testosterone as a non-invasive way to screen for hypogonadism. In another study, Morley et al. compared the usefulness of three different screening questionnaires: the St. Louis University Androgen Deficiency in Aging Male (ADA); the Aging Male Survey (AMS); and the Massachusetts Male Aging Study (MMAS). In general they found that some of the questions were well correlated with bioavailable testosterone and calculated free testosterone, but not with total testosterone. They found the ADA and the AMS questionnaires to be sensitive but not specific. The MMAS was neither sensitive nor specific.

Black et al. did a small study (n of 38 males who actually completed the study) in which they studied the effects of a 3-month therapeutic trial of testosterone replacement. They undertook this precisely because of the difficulties in actually pinpointing a diagnosis of symptomatic late-onset hypogonadism (SLCH). Their conclusion in what was essentially a pilot study was that further research with larger sample sizes and “other biochemical measurements” is necessary before therapeutic trials with testosterone can be definitively recommended for men with SLOH and without contraindications.

Snyder, in his 2004 New England Journal of Medicine “Perspective” piece reminds us that: “An essential but still unanswered question is whether this decrease in the testosterone concentration is physiologic, perhaps conveying a benefit, or pathologic, causing harm.” 10(p.441)

Another essential, but also unanswered, question is whether reversing this decrease in testosterone concentrations will exacerbate the testosterone-dependent diseases to which elderly men are prone, including prostate cancer, benign prostatic hyperplasia, erythrocytosis, and perhaps sleep apnea. No data, unfortunately, are available with which to answer this question. 10(p.441)

Snyder proceeds to discuss the report of the Institute of Medicine’s Committee on Assessing the Need for Clinical Trials of Testosterone Replacement Therapy, Testosterone and aging: clinical research directions. The authors of this report, according to Snyder, actually do not even feel that a long-term study to determine the risks associated with testosterone replacement [is presently warranted]. Instead, the committee recommended first performing short-term, randomized, placebo-controlled studies of the effect of testosterone on several outcomes in elderly men whose testosterone concentrations are below 300 ng per deciliter and then, only if the short-term studies demonstrate efficacy, performing a long-term study to evaluate the risks. 10(p.441)

Snyder then outlines four basic principles to help guide practicing physicians in the interim period. In brief these are:

1. The criteria for establishing a diagnosis of hypogonadism should be “more stringent in the absence than in the presence of a disease that is known to cause hypogonadism, such as a pituitary macroadenoma, and should be more stringent in an elderly man — say, older than 65 years of age — than in a younger man.”
2. “To limit treatment to men who are more severely hypogonadal, on the premise that those men are more likely to benefit.”
3. Serum testosterone levels need to be very carefully monitored in patients receiving replacement therapy.
4. “To screen for testosterone-dependent diseases before initiating treatment and to monitor patients for their development during treatment.” 10(p.442)

In summary, there is clearly a dearth of evidence-based studies that seek to clarify the evaluation and treatment of hypogonadism in elderly males. Controversy exists at every level, including: 1) whether or not a clinical syndrome of hypogonadism even exists; 2) what the features of that clinical syndrome are; 3) which diagnostic measures are most appropriate (many authors refer to free or bioavailable testosterone as the gold standard while others, for example Snyder hold that assays for total testosterone are much more reliable and available than assays for free testosterone); 4) whether or not testosterone therapy is effective in alleviating symptoms; 5) which formulations, dosages and routes of administration are optimal; 6) whether or not testosterone therapy is safe. (Careful monitoring for prostate malignancies and a contraindication to its use in men with a history of prostate cancer is advocated by most—some, however, such as Rhoden and Morgentaler— conclude: “After 1 year of TRT men with PIN do not have a greater increase in PSA or a significantly increased risk of cancer than men without PIN. These results indicate that TRT is not contraindicated in men with a history of PIN.” 11(abstract); and, finally, 7) whether and which older men should or should not be screened for hypogonadism.

In the presence of such a complete lack of consensus on any aspect of definition, evaluation, or treatment, it does indeed seem puzzling that more definitive studies were not recommended by the Institute of Medicine’s Committee on Assessing the Need for Clinical Trials of Testosterone Replacement Therapy. Snyder’s implication and Harman’s frank assertion that the committee’s “recommendation, if adhered to, is likely to delay, rather than foster, progress in this important area” 12 seems apparent.

References