Testosterone replacement therapy

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The recent introduction of a variety of novel preparations have stimulated the medical community to consider their application in a subpopulation of aging males.

Androgen deficiency in the aging male (ADAM) or andropause is purported to be a common condition in men over 40, characterized by a constellation of symptoms including increased mental irritability, decreased muscle strength and libido, and vasomotor manifestations loosely correlated with falling testosterone levels. In addition, the accompanying effects of this hypogonadal state include osteopenia and possibly increased cardiac morbidity (1).

If we use current acceptable testosterone ranges, 7% of men aged 40 to 50 years, 20% aged 60 to 80 years and 35% of men over 80 years of age would have below-normal serum testosterone (2). Not all of these men will exhibit the ADAM symptom complex, although few men over the age of 40 years will not admit to decrease in sexual appetite and energy levels, contributing to the difficulty in establishing a proper diagnosis. (3) Without significant scientific evidence to support this therapeutic intervention, physicians have been asked to consider treating these men with testosterone. In addition to declining testosterone levels with age, many other factors such as a decrease in adrenal hormones (dehydroepiandrosterone sulfate) and growth hormone as well as a decrease in physical activity, are thought to play a role in these age-related changes (4).

Little is known about the outcome of longterm treatment of older men with testosterone. In elderly hypogonadal men, testosterone administration positively affects biochemical markers of muscle and bone metabolism and can increase lumbar spinal bone density (5). We do not have clear evidence that this translates to a reduction in age-related falls and fractures. At the present time, there are good therapeutic interventions supported by prospective well-controlled trials that can increase bone density to the same degree as testosterone administration without the need for daily drug administration. (5).

The relationship between testosterone and libido is strong but inconsistent. Despite the significant difference in bioavailable testosterone levels in older men, complaints of decreased libido are rare; the most common sexual complaint being erectile dysfunction (ED). Depression is the most common clinical condition producing decreased libido in all ages (6). Depressed men with significantly reduced testosterone levels may benefit from addition of testosterone to antidepressant therapy, but again the results are variable and scientific support scarce. There is considerable overlap in the symptom complex between depression and ADAM and urologists, more comfortable with surgical problems and solutions, may not be the best suited to differentiate these two conditions.

While there is little evidence that testosterone replacement increases the risk of prostate cancer, there are no controlled trials that suggest this practice is entirely without risk (7). Testosterone is contraindicated in the presence of prostate cancer and longterm administration places a significant burden on the physician to insure their patients do not develop prostate cancer while on testosterone. While evidence is lacking that benign prostatic hyperplasia may be accelerated by testosterone administration, aromatization of excess testosterone to estrogens could exacerbate underlying breast carcinoma (1). Other potential side effects of longterm testosterone administration include an increased hematocrit, exacerbation of sleep apnea, gynecomastia, suppression of spermatogenesis and fluid retention (7).

The lack of consensus on what constitutes the diagnosis of biochemical hypogonadism further weakens our diagnostic and therapeutic abilities. Low levels of testosterone, free testosterone or bioavailable testosterone correlate poorly with andropausal symptoms (8), and some authors suggest that the symptoms alone are sufficient for a trial of testosterone therapy in the presence of low normal levels. Without good endpoints, a trial of therapy serves little diagnostic purpose and is costly. Until then, physicians who treat andropausal patients may consider themselves principal investigators in a poorly controlled, prospective study paid for by the government and their patients.

No validated tools exist to assist the physician in their assessment of andropause and the evaluation of treatment response. The Morley Questionnaire appears in a number of educational publications and papers but has not been appropriately validated and is not designed to assess treatment response (9). This tool has a sensitivity of 88% and a specificity of 40%. These figures suggest that, if widely used by physicians, a false positive diagnosis could occur in up to 40% of men tested if applied as a screening tool. Further work is necessary to develop a more specific questionnaire that is sensitive to treatment effects and can be used as a diagnostic aid.

The cost of widespread testosterone replacement for men would be astronomical, the cost effectiveness unknown. In addition, deficiencies in our diagnostic capabilities insure that a large number of men will be unnecessarily exposed to

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three to six months of therapy with no change in their initial complaints.

Our heightened awareness of Erectile Dysfunction (ED) has clearly benefited the testosterone industry by increasing the number of men discussing sexual difficulties with their physicians. Unfortunately, testosterone has traditionally been associated with sexual performance and is a frequent request of patients pursuing improvements in their sexual health. The success of testosterone therapy in men with reduced libido is variable and dependant on an appropriate initial diagnosis (10). The effort necessary to sort out the other psychosocial and lifestyle issues to insure a proper diagnosis is not one physicians readily accept. ED patients are even more resistant to counseling and lifestyle modifications (10). It is likely that the same pattern will be seen in the andropausal patient.

Why then, in the face of a poorly defined clinical entity (ADAM), with no reliable marker (serum testosterone determinations), the absence of a tool to determine treatment benefits and with little longterm efficacy and safety data when used in this population, are we being asked to consider horomone replacement therapy for men. Urologists have little background in the assessment and treatment of osteoporosis or depression and few are willing to spend the necessary time counseling these patients. Is the explosion of testosterone propaganda a result of an unmet need identified by physicians or an industry driven syndrome? In my opinion it is the latter.

Testosterone is a drug looking for a broader indication. In clearly hypogonadal men with symptoms of testosterone deficiency and an understanding of the clinical endpoints expected with treatment, replacement therapy can provide an improvement in quality of life, restoration of normal sexual function, and may reduce the longterm sequelae associated with testosterone deficiency, such as osteoporosis. This patient population is relatively easy to define; the andropausal population is not. Defining it by a trial of therapy is not only unscientific but also unsafe. The development of new delivery systems for testosterone has been the major impetus for its use, not the demand for a solution to the ADAM problem. Fortunately, we have begun to narrow our indications for testosterone replacement as we examine our patients response to therapy.

Properly controlled clinical trials, together with the development of validated instruments and a reliable marker for ADAM, is necessary before testosterone therapy should be accepted. A scale similar to the International Index of Erectile Function (IIEF) that includes all affected domains would be invaluable in assessing and treating this population, Monies spent on 'educational forums' for andropause, continuing medical educational events and conference dollars targeted to spreading the spin on testosterone therapy could, in part, be directed to the scientific community. There has been a significant 'direct to consumer' advertising effort and a variety of popular web sites written by physicians and supported by industry touting the potential positive effects of testosterone in all men. Physicians rely on industry to assist them with their educational needs and 'opinion leaders' to help design these courses to provide useful, evidence based knowledge. At the present time, our opinion leaders have little scientific ammunition to bolster the barrage of testosterone applications. Many of the symptoms associated with the andropausal syndrome can be alleviated with attention to diet, exercise, education and counseling. Osteoporosis can be treated with a number of agents and it is unlikely that the cardiac risk argument will withstand the test of time. Unfortunately, both physicians and patient prefer an 'interview ending' prescription rather than a reconfiguration of their lifestyles.

Not until an effort is made to provide physicians with supportive clinical data and validated assessment instruments necessary to safely introduce testosterone therapy to the targeted populations should we embrace the concept of Andropause. Physicians should insist that industry, not the patient, pay the price of admission.

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