Testosterone Deficiency in Men: **New Treatments for Andropause**

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Anyone would recognize Max as an alpha male: successful in business, handsome and athletic, a captain of the football team in high school (where he was voted "most likely to go to Congress"), and a golf club champ as an adult. That was before Max was 50. Then, decreased enthusiasm for work lead to a lack of attention to detail and feelings of aggression in his business, which ultimately resulted in bankruptcy. Max gained weight and began to notice a midriff bulge that had never been present before. He felt a pall of fatigue and woke each day with sore, stiff muscles. His golf handicap doubled, and he began to lose to less apt golfers whom he had regularly beaten in the past. To make things worse, he experienced impotence for the first time and was rapidly reaching the "I don't care about anything" stage. Max was experiencing a defeating depression.

The results of a visit to his doctor for a physical examination were startling. Max's blood pressure was elevated for the first time, and his cholesterol level had increased 60 points. When the physical examination had been completed, Max asked what had caused his change in energy and sore muscles. He did not mention the incidence of impotence because he was too embarrassed.

Max's testosterone level was not evaluated as part of his physical examination, yet every symptom that he had experienced was a classic indication of testosterone deficiency. An undetected decline in testosterone will continue, and an increased risk of early death from stroke, heart attack, diabetes, or hypertension could result for Max and for many men with similar symptoms. Testosterone deficiency is easy to diagnose and to treat, and though it is very common, few patients recognize related signs or symptoms. Almost complete resolution of symptoms results from early initiation of treatment.

"You're getting old." "You're not as young as you used to be." Statements like those are often said to men in their middle-to-senior years who experience physical and emotional changes that affect them in various ways; changes that seem inevitable and just a natural part of aging. Can they be prevented? Although aging cannot be halted, recent research indicates that much can be done to modify or retard the process. The physical and emotional symptoms experienced by middle-aged men have been referred to as "andropause" or "male menopause." But unlike menopausal women, men experience andropause for many different reasons. No defined pattern of symptoms indicates andropause, which presents a problem for practitioners and patients. The process of andropause has not been defined, and as a result, the long-term risk-benefit ratio of correcting the condition has not been determined.

Why has a condition experienced by such a large number of men remained obscure? There are probably several factors: Many men are reluctant to discuss andropause or are not willing to acknowledge the symptoms that it produces, and many are hesitant to admit to episodes of depression, loss of libido, or (particularly) sexual dysfunction. The decrease in the testosterone level is usually slow (approximately 1% per year). This decline is so gradual that physical, mental, or emotional changes are hardly noticeable until years have passed. Negative information in the popular press and in medical literature regarding "steroid abuse" frequently results in skepticism about a new syndrome or a new treatment. There are valid reasons to be cautious about the use of anabolic steroids (even the prescription forms) such as methyltestosterone because liver problems, hypertension, and cardiovascular complications have been reported to result from high doses.

We must differentiate between synthetic androgens such as methyltestosterone and the basic natural hormone testosterone. The literature[1] indicates that natural, pure testosterone (USP) does not result in the same side-effect profile as that produced by synthetic substituted androgens. In our opinion, there is increasing evidence that testosterone administered in physiologic doses produces few negative side effects. The presence of prostate cancer and the relatively uncommon presence of breast cancer in men are the only absolute contraindications to the use of testosterone supplementation in men.[1] Several studies[2-5] indicate that testosterone is a promising treatment for men with osteoporosis and depression and that testosterone replacement therapy minimizes the incidence of stroke and heart attack.

Of course, testosterone supplementation is not a panacea; it does not reverse all signs of aging, and not every man with testosterone deficiency should receive hormone replacement. Not all men suffer from a steep decrease in the testosterone level; many maintain a level that is well within the normal range and feel as fit as ever. As a group, those men are likely to survive to the latter days of their golden years and may have a quality existence long after their peers who have a low level of testosterone have died! Is natural hormone replacement with testosterone the "fountain of youth" for middle-aged men? No, but it may be one of the keys to "quality aging" and to living to the age dictated by individual genetics.

What should a man who suspects that he may be deficient in testosterone do? The first step is to undergo a physical examination by his physician. That examination should include determining the levels of total and free testosterone, estradiol, prostate specific antigen (PSA), lipids, and glucose as well as the results of a complete blood count. If the level of testosterone is low-normal or deficient, other testing to determine the level of follicle-stimulating hormone, luteinizing hormone, and (possibly) prolactin should be undertaken to identify the cause of the deficiency. In addition, evaluations of thyroid function and iron status should be performed, and a review of medicines taken and health changes should be assessed. Treatment can be initiated after a diagnosis has been made.

The goal of treatment is simple. The deficiency must be corrected, and laboratory values must be monitored to ensure that treatment restores the testosterone level to the normal range. Cholesterol and blood glucose levels should be monitored, as should an improvement in symptoms that show clinical response. Important indications of successful therapy include an increase in strength, stamina, and energy level, all of which reflect improved muscle tone and muscle function; increased libido and sexual responsiveness; the return of mental acuity; improved mood; and a greater zest for life. Those factors are true quality-of-life indicators and are essential to good

health, which can be enhanced by normalized hormone levels.

There are several treatment methods of safely and effectively normalizing the level of testosterone: boosting production by stimulating the pituitary, directly stimulating the testicles, or replacing deficient levels by means of hormone replacement. Sometimes, correcting lifestyle or health problems or changing medications that depress testosterone production is the best treatment. Sensible weight management, exercise, and correction of deficiencies (such as a low level of zinc) are important considerations. Identifying and treating iron overload or hypothyroidism, which are reversible causes of testosterone deficiency, are appropriate therapy in younger individuals. For a middle-aged 50-year-old patient, increasing the level of dopamine in the brain may increase the feedback loop that leads to the restoration of testosterone production; in such patients, this may be a better approach than quick replacement, which suppresses endogenous production. Natural herbal treatments such as ginseng are popular, though long-term studies of such alternative approaches are not yet conclusive.

Supplementation with "prohormones" such as dehydroepiandrosterone (DHEA) or androstenedione is a subject of recent attention. DHEA has been extensively researched, but conclusive evidence of its effect in boosting the level of testosterone has not been established. Furthermore, supplementation with androstenedione has shown little effect in restoring or boosting the testosterone level to within the normal range. However, topical preparations containing other prohormones have better testosterone-restoring effects than those of oral androstenedione alone. Practitioners must be aware of supplements used by their patients, because some preparations may also increase estrogen levels, which can ex cessively increase the risk of side effects.

After the diagnosis of testosterone defi ciency has been established, hormone re placement options can be reviewed fo each patient. Among the replacement form used are intramuscular injections (usuall of the cypionate or enanthate esters); sub lingual troches or lozenges; topical creams gels or lotions; and implantable testos terone pellets. All replacement forms hav some advantages, but several have liabili ties or limitations.

Intramuscular injections have the mos unphysiologic pharmacokinetics of all dos ing forms for testosterone and are frequentl associated with erratic effects. This form o therapy is the most common and also th least effective. Intramuscular injections d not release a constant level of testosteron over 2 to 3 weeks. Instead, the patient treat ed with that form of therapy may exhibit

Serum and Saliva Levels of Testosterone

Serum Levels	Laboratory Reference Range	Optimal Range
Total testosterone	200-825 ng/dL	600-750 ng/dL
Free testosterone	35-195 pg/mL	140-175 pg/dL
Saliva Levels	**Laboratory Reference Range**	**Optimal Range**
Bioavailable testosterone	100-475 pmol/L	350-400 pmol/L
Patient age		
20-29	409-478 pmol/L	
30-39	301-398	
40-49	201-249	
50-59	180-236	
60-69	170-184	
70-79	97-173	
Free Testosterone	40-200 pg/mL	

Note: Saliva levels from topical administration may be higher that those listed above.

Serum and Saliva Levels of Estradiol

	Laboratory Reference Range	Optimal Range
Serum Level	0-50 pg/mL (0-5 ng/dL)	20-30 pg/mL (2-3 ng/mL)
Saliva Level	0.76-2.18 pg/mL (2.8 - 8.0 pmol/L)	0.76-1.63 pg/mL (2.8 - 6.0 pmol/L)

high level of testosterone during the first week after the injection and a low level during the subsequent week. A high level of testosterone is converted to excess estradiol, which results in poor erectile function and possibly gynecomastia.

Testosterone is well-absorbed sublingually or buccally without a "first-pass" effect. Thus troches, tablet triturates, or drops are effective means of dosing. Because of the short serum half-life of testosterone, those doses may have to be administered 3 to 4 times a day.

The implantation of pellets in subcutaneous tissue is one of the oldest forms of replacement. Although this form of therapy requires a minor surgical office procedure, implantation must be repeated only every 4 to 6 months. The stable, slow release produced by this form of replacement is often appropriate in older, less-compliant patients who require sustained hormonal support.

Testosterone can be applied topically in gels or creams or supplied by transdermal patches. The patches that have been commercially available for nearly a decade are poorly tolerated by patients because they irritate the skin and they are expensive. In addition, the level of testosterone that is absorbed from the patches is relatively low, which also results in noncompliance. For several years, compounding pharmacists have been preparing hormone replacement therapy in cream or gel vehicles that have resulted in positive outcomes for patients. Recently, a commercial gel with a specific indication for men with a low testosterone level was introduced. Studies[6] indicate that this type of dosing is pharmacokinetically stable and can produce an effective level of testosterone. The optimal dose and the optimal volume for delivering that dose have not been determined. A recently published study[7] demonstrated that once-a-day dosing to a large surface area produced results comparable to those of 4-times-a-day dosing to a smaller area. Information such as this is vital to producing better results for our patients.

Who are the patients that need testosterone replacement, and how can we help them? The April 24, 2000, issue of *TIME* magazine featured testosterone supplements and andropause as subjects of the cover story. A major television news network aired a similar feature more recently. Today, more and more men are aware of the entities of andropause and testosterone deficiency. Those conditions, like depression and erectile dysfunction, are being recognized and successfully treated.

The most likely sources of first-line diagnosis and therapy are the patient's primary care provider, internist, or family physician. Those practitioners most often observe the patient's range of symptoms and can identify them as characteristics of hormone deficiency.

To paraphrase an old adage, "They say you're as old as you feel. I feel old." Perhaps for many men who can benefit from hormone replacement therapy, that saying will no longer apply.

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