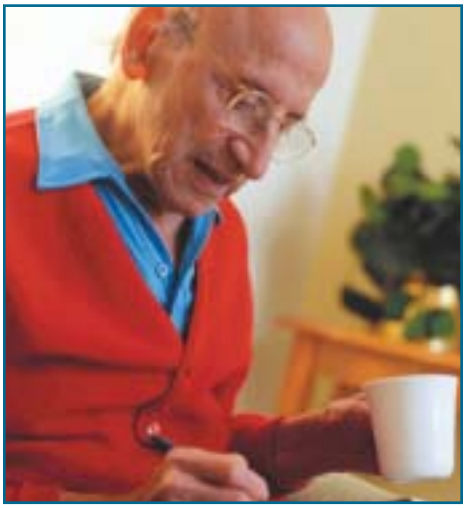

Screening, Diagnosing and Treating Androgen Deficiency

Androgen deficiency states represent significant clinical problems that cannot be overlooked or dismissed as a matter of simple aging. With a careful and educated use of androgen replacement therapies, patients can live more productive and healthier lives.

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The past 20 years have seen a surge of interest develop in androgens and androgen-related clinical problems. This previously misunderstood field, originally plagued with suspicion, had been shoved into the back pages of medical journals. Now a front-page runner for the last decade, a week will not go by without blatant media coverage espousing the supposedly new found benefits of treating androgen deficiency. Although some apprehension remains, this field has deservedly been thrust into the spotlight.

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It is difficult to realize the first scientific observations in the field of andrology date back more than 100 years, before terms such as “hormone” and the field of endocrinology ever existed. Even when a Nobel Prize was awarded to Butenandt and Ruzicka for their pioneering work on testosterone synthesis in the late 1930s, most of the clinical applications of

androgen treatment were still at the level of unscientific charlatanism, such as testicular extracts and implantations of monkey glands into humans. Despite this and further damage to the androgen field caused by athletic and bodybuilding misuse, progress slowly continued. Even today, andrology encounters public apprehension and skepticism due to the disreputable status of androgens equated with the widely publicized performance-enhancing doping of athletes.

General medical and scientific observations aside, the distinct matter of andropause was brought into moderate light more than 20 years ago, although we can trace back some early scientific studies into the first half of the 1950s. Andropause, as a coined phrase from these early studies, is a misnomer that, unfortunately, separates females from males in the field of androgen deficiency (AD). Better understanding of the role of androgens in the body has emerged over the years, however, along with an improved understanding of the clinical problems AD syndromes cause in both sexes.

Relentless pioneering work of multidisciplinary research has defined AD as part of a significant medical pathophysiological condition with far-reaching effects on human health. It is indisputably accepted today that androgens play a crucial and essential role in preserving physical and mental health, much wider and deeper than originally accepted assumptions of androgen's inherent function in sexuality and male biology would have us believe. The preservation of optimal psychological functioning, its effect on aging and the protective role androgens play in several key illness groups (*i.e.*, diabetes, cardiovascular disease [CVD], rheumatoid arthritis, osteoporosis and systemic lupus) demonstrate the wide-reaching effect androgens have in maintaining health.[1-3]

Just as the original discoveries related to menopause prompted the evolution of estrogen replacement therapy (ERT), the focus on the role of androgens and testosterone have created such terms as "male menopause," "male climacteric," "andropause" and "partial androgen deficiency in the aging male (PADAM)" in the field of andrology. Along came recommendations for androgen replacement therapies, as well as concerns regarding their long-term effects on the body. Questions raised

Summary

Screening, Diagnosing and Treating Androgen Deficiency

- Androgen deficiency (AD) syndromes are relatively common in both sexes. More epidemiological research into female-related AD and its related clinical presentations remains to be conducted. The level of insight we now have into male-related AD, however, has allowed a safe incorporation of testosterone replacement therapy (TRT) into the office practice.
- Treatment options for TRT include the following: oral, transdermal and intramuscular.
- In men, the focus for follow-up should be on the patient's prostate health and possible changes in hematocrit values.
- Young female patients may present with a history of taking the birth control pill for many years, with resultant ovarian function suppression.
- There are several suitable oral, injectable and local testosterone compounds currently available for treatment of female AD.

included: Is it physiological? Is it safe? What about its effect on the liver and prostate gland? There has also been concern over androgen replacement therapies in relation to cancer, serum lipids and erythropoietin. Fortunately, most early concerns and fears were unfounded. The original problems associated with testosterone replacement therapy (TRT) were resolved, and TRT is now considered a safe, beneficial and appropriate form of treatment for various androgen deficiency conditions.[4,5]

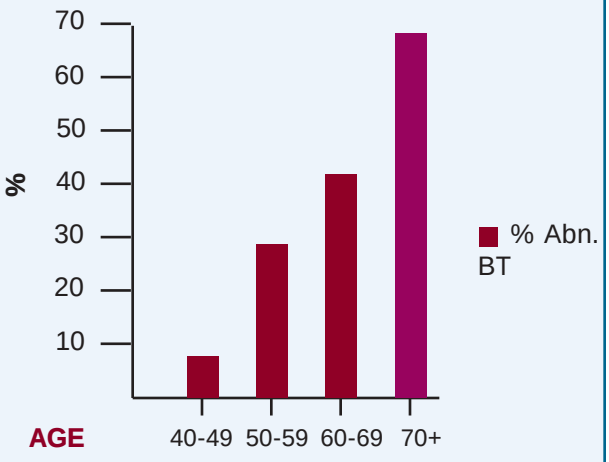
The production of testosterone in a healthy male continues uninterrupted until death, although it does decrease slowly with age. This is contrary to a female undergoing menopause, where estrogen production suddenly decreases following the ovarian involution. A young male produces an average of 7 mg of testosterone per day, while a male in his 60s produces approximately 4 mg. This should not cease or undergo significant reduction, unless some pathology develops that affects testosterone production.

The knowledge of age-related decreasing sexual potency is well known. While studying male erectile dysfunction (ED) at the Ottawa Civic Hospital in the late 1970s, the author's multidisciplinary study of 220 men revealed the presence of endocrine and metabolic problems in 44% of the subjects complaining of ED, with the mean age of subjects being 50.3 years.[6] Numerous studies detailing the effects of age on testosterone levels have shown some decreases are to be anticipated as age advances. Significant individual variations exist, however, due to other factors being present, affecting the absolute levels of circulating and biologically active hormone. A recent study of 316 Canadian physicians aged 40 to 82, conducted by J. Morley of St. Louis University (Figure 1), indicate a fairly classic age-related decrease of bioavailable testosterone levels with progressing age. The selection of bioavailable testosterone (BT) over the standard "total" or "free" testosterone levels for the study of BT represents loosely bound to albumin plus free testosterone. This reflects our current knowledge of which testosterone test most accurately represents the biologically active values. Note that in the BT test, the biologically inactive testosterone bound to sex hormone binding globulin is not measured.

Figure 1

Androgen Deficiency in Canadian Male Physicians

The overall rate of abnormal BT levels in a sample of 40- to 70-year-olds was 25%.



Abn = abnormal; BT = bioavailable testosterone
Adapted from: Morley J, Charlton E, Patrick P, et al: St. Louis University Study, abstract (P2-649), presented at Endocrine Society meeting, June 1998.

Common Causes of Androgen Deficiency

The following list outlines the common causes of androgen deficiency in men:

- Age over 50;
- Decreasing steroidogenic activity of the gonads (*i.e.,* due to vascular insufficiency);

Since many females present with AD symptoms at quite a young age, sometimes decades before the menopausal age, possible AD is usually not considered.

- Increasing levels of sex-hormone binding globulin (SHBG);
- Increasing peripheral conversion of testosterone;
- Pituitary or hypothalamic feedback-loop failure;
- Decreasing receptor sensitivity;
- Stress;
- Alcoholism;
- Liver disease;
- Estrogen or prolactin excess;
- Low fat diets; and
- 47 XXY syndrome, dysgenetic testes, secondary testicular atrophy.

Androgen production in females does not parallel the drastic physiological fall of estrogen in perimenopause and menopause. Their testosterone production remains, albeit at a diminished level. It has been reported the testosterone levels of a woman in her 40s is about half of the amount found in a woman in her 20s. In surgical, medical or disease-related hypoandrogenic states, symptoms of AD vary, depending on age and estrogen presence.[7]

AD syndromes are relatively common in both sexes. More epidemiological research into female-related AD and its related clinical presentations, remains to be conducted. The level of insight we now have into male-related AD, however, has allowed a safe incorporation of TRT into the office practice. The following list of symptoms, usually associated with AD, represent the author's observations and results from clinical experience in working with hypogonadal men for 20 years.

Diagnosis and Treatment

The following are symptoms to look for when forming a diagnosis of androgen deficiency:

- Sensation of loss of "well-being;"
- Diminished activity level, endurance and pace;
- Decreasing interests and drive;
- Decreasing/diminished or lacking sexual drive and desire;
- Sexual anhedonia, possibly anorgasmia, erectile dysfunction;
- Irritability and dysphoria;
- Impaired cognitive acuity (learning, concentration, attention span);
- Impaired stress tolerance;
- Sarcopenia (loss of muscle mass) and osteopenia; and
- Frailty and general weakness.

Screening. Pre-treatment screening involves:

- History and physical;
- Baseline digital rectal examination (DRE) and prostate specific antigen (PSA) level; and
- BT (or free testosterone) level, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin and hematocrit levels.

If the BT level falls at or below 3.5 nmol/L and the clinical picture points to AD, treatment should be initiated.

Treatment. Treatment options for TRT include the following:

- *Oral:* Testosterone undecanoate;
- *Transdermal:* Permeation-enhanced testosterone;
- *Intramuscular (IM):* Testosterone cypionate and testosterone enanthate.

Each particular route has been proven effective. Aspects, such as cost and preference for ease of administration, usually determine the choice. Although each mode has its distinct advantage over the other, there is no evidence of a significant difference in clinical application to warrant a "preferred" choice among the three. The easiest route seems to be the oral mode, especially since concerns pertaining to potential liver-related difficulty (associated with use of halogenated steroids) has been eliminated (the 17-alkylated or halogenated compounds are now considered obsolete and are no longer recommended). The following are the treatment guidelines for all three routes of administration:

Transdermal. Initiate treatment with one 2.5 mg patch to be applied at bedtime and worn for 24 hours. Increase the dosage to two 2.5 mg patches nightly if required (as judged by clinical response). The free testosterone level should be obtained before dosage adjustments are made. Up to three 2.5 mg patches per 24 hours may be required in corpulent males, due to both body mass and testosterone conversion into estradiol by aromatase found predominantly in fat tissue.

Oral. Start with a 40 mg testosterone undecanoate tablet three times daily (tid), with meals. Some dietary fat in the diet is required for adequate absorption and transfer. This mode may not be suitable for individuals on low-fat or no-fat diets. Follow up by testing the patient's free testosterone level at three months or before considering a dosage adjustment (the average required dose is 160 mg per 24 hours).

IM. Start with either testosterone cypionate or testosterone enanthate at 150 mg per two-week interval, by deep IM injection into the upper gluteal site. Alternate sites with each subsequent injection. Decrease or increase dosage by 25 mg, depending on the patient's clinical response and free testosterone level. A free testosterone test should be performed initially on the fifth post-injection day, then following the third injection, and when checking the PSA level. Supraphysiological levels of free testosterone obtained on the fifth post-injection day indicate the need for a dosage adjustment.

Remember, a "kick-start" effect has been clinically encountered and the amount of the original TRT may have to be adjusted, reflecting the changing endogenous production. In the presence of an excellent response to treatment, it is appropriate to extend the interval between the injections. This improved response may relate to a changing receptor sensitivity level, along with the treatment's progress. Appropriate dosage adjustments also should be followed for the oral and transdermal routes of administration.

The focus for follow-up should be on the patient's prostate health and possible changes in hematocrit values. Compare the PSA level with the baseline at three months initially, and follow with tests every six months. It is also recommended to request hematocrit and a free testosterone level at the same time.

Adherence to regular DRE examinations is absolutely essential, since some prostate-related

pathologies are not always reflected in changing PSA values. Follow the initial (baseline) DRE with a repeat at three months, followed by re-examinations every six months for the duration of the TRT.[8] Even with the PSA level below two, 8% of incipient prostate cancers can be missed.[9] Proper adherence to DRE follow-up protocol should correct much of the PSA error. Suspicious findings should be followed *via* ultrasonography or a urology consultation, as required. In some AD males with smaller prostates, the TRT may trigger prostatic enlargement, usually modest and insignificant. Such size increases of the prostate gland usually occur in aging men with normal-for-their-age testosterone levels. It is common for PSA values to show a slight increase during the treatment, reflecting this fact.

Contraindications. The following lists absolute contraindications to TRT treatment:

- Existing or suspected carcinoma of the prostate;
- Breast cancer;
- Testicular cancer; and
- Prostate hypertrophy with severe urinary obstruction.

Relative contraindications include:

- Prostate hypertrophy with mild to moderate symptoms (LUTS);
- Sleep apnea;
- Nephrosis;
- Hypercalcemia; and
- Severe cardiac decompensation with edema.

If properly indicated and safely administered, TRT can a have significant affect on AD patients. The following are some benefits, as reported by various studies:[10,11]

- Improved sense of well-being;
- Improved virilization and libido;
- Improved strength and stamina;
- Preserved bone mass;
- Improved muscle mass;
- Reduced abdominal fat;
- Reduced cardiovascular disease risk;
- Preserved cognitive functions; and
- Improved affective state.

Female Androgen Deficiency

As noted previously, the term "andropause" separates females from the males in AD-related matters. Yet, a physician who has had the opportunity to work with both sexes in a clinical setting involving androgens will immediately recognize the similarities in pathophysiology, clinical presentation and symptoms. The level of biologically active testosterone in menopausal females is not investigated as a matter of usual course and treatment. As such, little is done about potentially significant AD states affecting females.

Since many females can present with AD symptoms at quite a young age, sometimes decades before the menopausal age, possible AD is usually not considered. Young female patients may present with a history of taking the birth control pill for many years, with resultant ovarian function suppression. The androgen/estrogen *versus* estrogen alone, or estrogen/progestin replacement therapy strategies are not new, as the original studies date back into the 1950s, yet relatively little has been done in this area on a clinical level. The evidence collected from the past 40 years can be best summarized by findings published by Morrie Gelfand, *et al*. Their results indicate only an estrogen/androgen replacement therapy corrected menopausal and libido-related problems associated with the hormonal deficiency and allowed patients to achieve a normal quality of life.[12,13]

Androgen replacement strategies for women have not yet been standardized. Much has been learned to date, so we can conclude that not all menopausal symptoms are corrected *via* estrogen/progestin therapy. As a result, androgen

replacement strategies are gaining a more prominent role in female health issues.[14-16]

In a clinical setting, the typical presentation of an AD female involves libido-related complaints. Loss of libido, anorgasmia and difficulty with sexual response are usual complaints. AD may also play a significant role in post-menopausal bone mass loss, while replacement therapies can alleviate various depressive problems, reduce nervous tension, palpitations, headaches and even improve memory functions and insomnia. The benefits of androgens on rheumatoid arthritis, lupus, insulin activity and cardiovascular (CV) protection are all known, as well.[17-19] Although the existing data are insufficient to recommend a prolonged androgen replacement therapy for post-menopausal women, short-term replacement strategies appear to be safe and without unpleasant, virilizing, side effects.[20,21]

A BT, or free testosterone level, will usually suffice in screening for androgen deficiency. Since global ovarian hypofunction or other regulatory system problems may be involved, more complete testing, including as much information about the patient's menstrual and sexual history, along with the serum levels of FSH, LH, prolactin, estradiol, progesterone and dehydroepiandrosterone (DHEA) should follow. An assessment of the psychogenic area and relationship issues is always appropriate, as is evaluation of the general life stresses and demands the female patient is facing. Depression and related states are known to cause significant anhedonia with possible neurohumoral (including hormonal) complications.

There are several suitable oral, injectable and local testosterone compounds currently available for the treatment of female AD. Pharmacy-prepared testosterone creams and ointments (1% to 2% testosterone cypionate in petrolatum jelly, or micronized testosterone in a suitable cream base in concentrations varied between 0.2% to 2%) can be administrated, as well. This topical treatment should be applied to the external genitalia, clitoral and labial region.

Oral testosterone undecanoate is recommended at 40 mg every second day, taken with a meal sufficient in dietary fat. The patient's free testosterone level and clinical response will determine dosage adjustments. Unfortunately, the proprietary 40 mg strength available was calculated with male patients in mind and does not reflect female needs. Up to 40 mg per day may sometimes be required, however, to correct the state of deficiency.

Empowering patients to regain lost functions, promote health, lead more productive lives and improve their sense of well-being is not to be confused with some misdirected search for the "fountain of youth."

IM TRT is known to cause hyperphysiological levels in the first few days following its administration, and, as such, has limited usefulness in female patients. Some of the original concerns regarding virilizing effects were related to the administration of proprietary formulas containing up to 150 mg of testosterone enanthate. The transient rise in the free testosterone level following recommended replacement dosage keeps the circulating, biologically active hormone levels close to the physiological range. As such, the virilizing effect is unlikely to be encountered. The additional difficulty with IM TRT in females is a possible inadvertent intra-adipose tissue injection with a subsequent loss of effect. Even a short course of

androgen replacement, however, can improve the "lost" libido.

The usual dosage of injectable testosterone cypionate or enanthate averages 30 mg, deep IM (with a range of 25 mg to 50 mg), every two weeks. As with some males, and especially so in younger females with AD, the so-called "kick-start" effect, representing probably both the biological and the psychological response, can occur after even a very short treatment.

Summary

In summary, the AD states, both in males and females, represent significant clinical problems that cannot be overlooked or dismissed as a matter of simple aging. Empowering patients to regain lost functions, promote health, lead more productive lives and improve their sense of well-being is not to be confused with some misdirected search for the "fountain of youth." With a careful and educated use of androgen replacement therapies, patients can live fuller and healthier lives. With the recent advances in the field of andrology, we now have the knowledge and the tools to detect, diagnose and treat such problems safely and effectively. Is it any wonder "andropause" is front page news? CME

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