

Holistic Approaches to Treating Andropause

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Andropause has been increasingly discussed in the media in recent years. Originally described as the “male climacteric,” in a *Journal of the American Medical Association (JAMA)*¹ paper in the mid-1940s, andropause has gained much attention lately among medical providers. In the *JAMA* study, Heller and Myers reported the benefits of testosterone replacement for relieving andropausal symptoms, thereby establishing the condition as an actual medical problem warranting replacement/treatment.

Although the case for andropause was established so long ago, several conflicting theories about the validity of andropause as an actual medical condition have prevented it from receiving much-needed attention, and a confusing label—“male menopause”—has also created problems with recognition.

In addition, relatively inconvenient treatments coupled with men’s notorious discomfort with seeking medical care (women visit the doctor roughly 150 percent more frequently than men) have kept andropause on the “back burner” of medicine.

The term andropause refers to a condition of lowered androgens, including testosterone, dehydroepiandrosterone (DHEA), and androstenedione. Incorrectly referred to as “male hormones,” these substances are found in both men and women. Peaking in the early to mid 20s, testosterone then begins a slow decline; each year thereafter the body’s total testosterone level declines roughly by 1.6 percent, free testosterone by 2 percent, and bioavailable testosterone by 2.5 percent.

Further compounding of this problem is a rise in sex hormone-binding globulin (SHBG) of roughly 1.6 percent per year.² Based on measurements of total testosterone, approximately 20 percent of men over 55 are considered hypogonadal³ and, when this condition is based on levels of bioavailable testosterone, 50 percent of men age 50 and over are considered hypogonadal.⁴

The Biochemistry of Andropause

The testes in a healthy young man will produce nearly 95 percent of his androgens, most of which is testosterone, at a rate of roughly 10 mg per day. The other 5 percent of androgens are

derived from adrenal-gland production of DHEA, a precursor molecule.

The stimulus for production originates in the hypothalamic-pituitary axis, where gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the release of two hormones, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), in the pituitary gland.

Luteinizing hormone drives the production of testosterone in the testes while FSH hormone affects spermatogenesis. Testosterone is metabolized further to dihydrotestosterone (DHT) by the ever-demonized enzyme 5-alpha-reductase (DHT is considered to be responsible for prostatic hypertrophy as well as male-pattern hair loss in genetically susceptible men)⁵ or it undergoes transformation into estradiol via the enzyme aromatase.

DHT binds with greater affinity to androgen receptors and therefore acts as a more potent activator (up to four times the strength) of testosterone receptors. Estrogens are also a factor in andropause; 25 percent of the estradiol (the most biologically active form of estrogen) produced in the male is derived from the testicles while the remaining 75 percent is produced from the abovementioned conversion process, mainly in adipose tissue, the brain, and the liver.

Nearly 98 percent of testosterone circulates bound to plasma proteins (and is thereby “unavailable”) whereas the remaining 2 percent, known as free testosterone, accounts for nearly all of the biologic activity of the hormone. Of the bound testosterone, 40 percent is tightly bound to SHBG while the remainder is relatively weakly bound to albumin and is therefore more readily available.

The term “bioavailable” refers to both the free testosterone and that which is bound to albumin.⁶ The amount of testosterone that binds with SHBG increases with aging thereby decreasing the amount of free testosterone.⁷ As testosterone levels fall, this stimulates increased production of SHBG by the liver; the estrogens in a man’s body will also increase SHBG. Increased levels of SHBG-bound testosterone lead to normal serum ranges of total testosterone, despite a relative deficiency in bioavailable testosterone.

When the body has excess androgens, SHBG will tend to be low, which results in normal levels of total testosterone but elevated levels of bioavailable testosterone.

Dosing Table

| Treatment | Dosing |
|----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| Hormone replacement therapy | Should be evaluated on an individual basis following extensive testing; typically introduced after all other means have been used |
| Testosterone replacement | Typical starting dose is 5–10 mg, topically |
| Dehydroepiandrosterone | 25–50 mg per day |
| Chrysin | 500–750 mg per day |
| Zinc | 30 mg per day ^a |
| Puncture vine or tribulus (<i>Tribulus terrestris</i>) | Variable; 250–1500 mg per day; standardized to 30–45% steroidal saponins (also known as furostanol) |
| Potency wood (<i>Muiria puama</i>) | 1–2 mL, extract, twice per day |

^aPatients should always supplement with copper when taking extra zinc.

The Aging Process

Aging is undeniably related to lowered androgen levels. Compared to female menopause in which hormone levels are attenuated in a much narrower period of time over 5–10 years, andropause is marked by a more gradual decline of androgens. Because of the gradual nature of the decline, other phrases, such as “androgen decline in aging males” [ADAM] or “alternative partial androgen decline in aging males” are used because the decline does not result in complete deficiency. When androgen levels are low enough to become symptomatic, this condition is then called andropause,⁸ which is technically defined as the natural cessation of the sexual function in older men.

The decline of testosterone in males that occurs with aging is associated with an increase in FSH and LH, albeit to a much lesser extent than seen in women.

Low testosterone levels with a transient rise in LH is suggestive of age-related impairment of GnRH.⁹ Because testosterone has only a supportive role in regulating spermatogenesis, the fertility of andropausal men may be minimally affected; this is evidenced mostly by increased numbers of sperm with abnormal morphology and impaired mobility.¹⁰

This situation is very different than that of women, in whom reproductive function is effectively ceased by menopausal-induced ovarian shutdown. The end result of sex-hormone deprivation in both genders is similar; loss of muscle, bone density, and cognitive function are common in aging patients, and they also develop increased risks for coronary artery disease and myocardial infarctions.

The exact mechanism by which androgens affect bone development and cognition are relatively unclear at this time; however, a definite protective effect has been observed.¹¹

Responsible for structural regulation of body proteins (and the development and maintenance of male genitalia), testosterone, at suboptimal levels, will initially lead to modest physical changes, including weakening muscles, bone loss, weight gain (primarily adipose tissue), and progressive facial aging. If testosterone is

continually low, changes in memory, impotence, general fatigue, and irritability result.

Decreased libido may be one of the first noted changes of age-associated testosterone decline in men. Declining testosterone and resultant loss of libido is not typically manifested by frustrated sexual urges, or complaints of frustration; most often this condition manifests as passivity. This can often lead to lack of interest in sex, visual sexual stimulation, business, competitive sports, and physical activity.

Typically, during a man's 40s or 50s, and sometimes even the 30s, testosterone production begins to decline noticeably. This is most often noted between ages 50 and 55. Symptoms are not universally experienced during andropause; however, the most frequently noted symptoms include mood changes accompanied by decreased well-being and changes in sexual function. One study of men age 60 and above revealed a 46-percent occurrence of loss of libido and erectile dysfunction, a 41-percent occurrence of general fatigue, and a 36-percent occurrence of memory loss.¹² The investigators noted, however, that correlation of symptoms with testosterone levels was highly variable and warrants further research.

Clinical Assessment

A detailed history, physical examination, and laboratory testing are necessary to rule out confounding factors and diagnose andropause correctly. Pertinent history questions should focus on the difference between loss of libido and impotence that results from erectile dysfunction.

Excessive alcohol intake can suppress androgen production. Several factors act as diagnostic confounders. Chronic illness and stress (physical and mental) can lead to a decline in testosterone levels. Pharmaceuticals, such as spironolactone, digoxin, and cimetidine, also may produce this effect. Conditions, such as insulin resistance, obesity, and diabetes, are associated with hypogonadism^{10,13,14} while anemia and hypothyroidism can produce fatigue and decreased libido. Other, more rare conditions, such as Kallman's syndrome, Klinefelter's syndrome, and Prader-Willi syndrome, that result in hypogonadism should be also be ruled out.

Treatments

Quite often, men suffering from symptoms of andropause are often treated for a specific, sometimes related, medical condition only. For instance, an andropausal man may be diagnosed with depression and given an antidepressant, rather than the doctor truly discerning the origin of the depression. With today's rampant prescribing of antidepressants to people that are not otherwise happy and content 100 percent of the time, this problem continues to be compounded (not to mention that antidepressants exaggerate loss of libido). Physicians may not see the entire pattern; but a holistic approach to the patient's entire symptomatology may include treatment with hormone replacement therapy (HRT), botanical medicines, nutrition, and exercise. Therapy is primarily focused on supporting and balancing hormone levels in the body.

Hormone Replacement

HRT Controversies

Similar to menopause, andropause can be treated with a combination of lifestyle, nutritional, botanical, and HRT approaches. The recent backlash against esterified estrogens used in combination with synthetic progesterone (progestin) molecules for treating menopause¹⁵ has led to a near-revolution and altered prescribing habits by physicians. Several events (popular media and research evidence) have led to a wave of interest in using bioidentical hormones to achieve hormonal balance.* An offshoot of this trend involves the use of hormone replacement in men. Among these are prohormones (DHEA, androstenedione, and pregnenolone) and testosterone. Combined with other natural medicines, treatment of andropause symptoms is rather successful but, as will be discussed, is not without controversy.

Testosterone Replacement

The knowledge base surrounding replacement of testosterone and androgens at physiologic levels in men with andropausal symptoms is much newer and less widely accepted in conventional medicine compared to the many accepted allopathic choices available to women. It is true that women, without a doubt, experience greater fluctuations and resultant symptoms because of the cyclical nature of female hormones. This has led in part to the vast "medicalization" of both the menses and menopause, wherein a solution to nearly any type of perturbation can be answered with one or more combinations of hormone replacement. Protocols and forms of HRT for men are quite limited by comparison.

Medicine has long held that prostate-specific problems, such as hypertrophy and cancer, are solely initiated by testosterone. However, a small body of evidence is accumulating that these problems may not be solely related to this hormone. This evidence indicates that accumulation of estrogen in aging may be the primary factor in the development of prostate disease later in life whereas testosterone and DHT play a secondary role, or act as promoters.¹⁶

Another study showed that there were no associations between testosterone, SHBG, or androstenedione concentrations and the incidence of prostatic carcinoma, further refuting the notion that androgens are the sole determinants of future prostate disease.¹⁷

What is more, with aging, testosterone levels begin to decline; yet at the same time, prostatic hypertrophy incidence elevates. The standard argument for this is that hypertrophy results from the cumulative effect of testosterone on the prostate gland. However, when focusing on incidence rates during the years of highest testosterone levels (20s, 30s, and 40s), when most of the exposure has occurred, this time period is associated with the lowest risk of prostate disease.¹⁸

Associated Andropausal Symptoms

- Erectile dysfunction
- Decreased libido
- Mood disturbances, including depression, irritability, tiredness
- Sleep difficulties
- Loss of muscle size and strength
- Osteoporosis
- Increased body fat
- Difficulty with concentration
- Memory loss

Diagnostic Confounders of Andropause

- Diabetes, renal failure, cirrhosis, anemia, or hypothyroidism
- Depression
- Alcohol abuse/poor nutrition leading to decreased albumin levels
- Abnormal circadian rhythm of testosterone
- Medications, such as cimetidine [Tagamet], digoxin [Digitek, Lanoxicaps,[®] Lanoxin[®]], spironolactone [Aldactone[®]], or antidepressants
- Acute stressors, such as surgery, severe burns, or accidents
- Vigorous athleticism
- Other confounders, including hypothalamic-pituitary tumors, Cushing's syndrome, hemochromatosis, Kallmann's syndrome, Klinefelter's syndrome, or Prader-Willi syndrome

The transformation (aromatization) of testosterone to estrogen occurs most readily in the fat stores of the body. Therefore, as one ages and gains weight, the aromatase enzyme system is fueled, resulting in elevated levels of estradiol, perhaps promoting prostatic disease. Conversely, as testosterone is metabolized via 5-alpha reductase, it is transformed into DHT, a molecule that androgen-related disease is currently blamed on.

When viewing the routes of metabolization of testosterone, we noticed that the two main avenues are via aromatase, leading to estradiol and 5-alpha reductase, leading to DHT. An unproven idea worth considering is the possibility that by blocking the 5-alpha reductase enzyme, one essentially creates a "backup" at this point in testosterone metabolism, forcing testosterone to be dismantled via aromatase, possibly leading to greater levels of estradiol and exacerbating the problem.

The problem is addressed by attempting to restore a more youthful balance between estrogen and testosterone by decreasing estrogen influence and increasing testosterone influence in the male body. This is referred to as increasing the testosterone-estrogen ratio. This is achieved with testosterone supplementation, often at doses of 5–10 mg per day, and taking steps to reduce estrogen load in the body, such as using phytoestrogens, dietary strategies, exercise, and nutraceutical options.

In addition, some physicians may augment this process by prescribing progesterone to men, further blunting estrogen's effect in the body. Prior to, and during, androgen replacement, a prostate examination should be conducted at the outset of therapy, and baseline and prostate-specific antigen levels should be measured, 3 and 6 months later and then every 6 months thereafter, if latent prostate symptoms develop.

*EDITOR'S NOTE: Bioidentical hormones for women are discussed in "Women's Health Update" by Tori Hudson, in this issue.

DHEA

DHEA has been promoted as a way to slow the aging process and several “symptoms” concomitant with the process. DHEA’s effects include reversing weight gain and increasing strength, endurance, cognitive function, immune function and overall energy levels. More specifically, however, DHEA is used to treat adrenal and androgen deficiency in aging adults. DHEA is produced in the liver and adrenal glands and testes in men. The majority of DHEA in the body exists in the sulfated storage form, DHEA-S. DHEA is converted into androstenedione, a main precursor of both androgens and estrogens.¹⁹

DHEA levels are typically higher in men than in women and tend to decline with aging in both genders. Interestingly, not all aging members of the population experience this effect; in approximately one third of adults, DHEA will increase with age.²⁰ DHEA supplementation appears to alter the gender-specific androgen–estrogen ratios; however, the amount of hormone that is elevated in each gender is different. Men will experience a large increase in estrogens but not as much in androgens when taking DHEA, and women who take the supplement will experience large increases in androgens but not in estrogens.²¹ Because of this, DHEA is quite often not an effective supplement for men who want to increase their androgen levels.

The androgen- and estrogen-producing effects of DHEA are thought to be responsible for the prohormone’s beneficial effects.²² In men who took DHEA for more than 24 weeks erectile dysfunction was reduced and the men had improved orgasm function, libido, and overall sexual satisfaction.²³

Much controversy surrounds the use of DHEA in both genders; studies to date have been generally small and of short duration. DHEA is a potent agonist of estrogen receptor–positive breast-cancer cells (and should therefore be used with caution in women).²⁴ In addition, DHEA is a prohormone; thus, one should be extremely cautious about using it because of its potential to increase cancer occurrence in both genders as a result of DHEA’s estrogen and testosterone precursor status.

Exercise

Declining testosterone has multifaceted origins and levels of the hormone can be augmented in numerous ways. Perhaps the most neglected medicine of all, exercise can improve an aging man’s testosterone levels (in addition to offsetting andropause-related bone loss, weight gain, muscle loss, and sleep and mood disturbances).

Moderate physical activity was shown to increase serum testosterone levels by 39 percent, SHBG by 19 percent, free testosterone by 23 percent, and total serum proteins by 13 percent, mainly during a period of exercise in one study.²⁵ The transient elevation of testosterone observed in this study was thought to be partly the result of increased SHBG concentration. Testosterone levels returned to baseline in the subjects after the exercise, indicating that hemoconcentration may have contributed partially to the subjects’ increased testosterone levels.

However, a separate study sought to challenge the observation

that perhaps this testosterone elevation was only related to increases in SHBG; investigators in this study concluded that, indeed, free testosterone does increase with moderately prolonged endurance-type exercise and this increase was not associated with a change in the binding affinity of SHBG.²⁶ Furthermore, the data from this study suggested that exercise-induced increases in testosterone was mediated by sympathetic stimulation of the testicles.

This effect has been demonstrated in studies that evaluated pre- and postexercise levels of LH, FSH, prolactin, testosterone, and free testosterone, showing no significant changes in LH, FSH, or prolactin either before or after exercise but showing an activity-related increase in both free and total testosterone.²⁷ Physical fitness has such far-reaching benefits for patients in nearly all conditions that it can, most assuredly, help the andropausal man. Exercise can not only offset associated andropausal changes but, at least temporarily, increase testosterone levels in serum. This may explain in part the widely observed exercise-related increase in mood seen among older athletes as well.

Aromatase Inhibitors

The previously mentioned enzyme, aromatase, is partially responsible for lowered levels of testosterone in men; it achieves this by converting the testosterone molecule into the closely related but vastly different estradiol molecule. (Aromatase works in both directions.)

Aromatase is a cytochrome P-450 enzyme that catalyzes the rate-limiting step in estrogen synthesis, from the conversion of androgens (androstenedione and testosterone) to estrogens. (Aromatase is also known as estrogen synthetase.) By inhibiting this enzyme, the transformation of testosterone into estradiol (and resultant decreased levels of testosterone) can be slowed. Aromatase inhibitors are useful for both men and women; in women, aromatase transforms stored androgens into estrogens. For this purpose, aromatase inhibitors are now used as anti-cancer agents for treating estrogen-dependent cancers.

Chrysin

Perhaps the most powerful of the naturally derived aromatase inhibitors, chrysin is thought to be one of the most potent inhibitors of human estrogen aromatase. Chrysin belongs to the flavone class of flavonoids and is derived from several plant species, the primary of which is *Passiflora coerulea*. Other sources include geranium species, such as lemon geranium (*Pelargonium crispum*), honey and bee propolis, and the *Pinaceae* species, which include pine trees.

The ability of chrysin to inhibit aromatization of androstenedione and testosterone has been demonstrated in vitro; however, in vivo studies are necessary. Other investigators have noted a phytoestrogenic effect²⁸ (binds weakly to alpha and beta estrogen receptors), and antioxidant²⁹ (inhibits xanthine oxidase and the consequent formation of uric acid and related reactive oxygen species) and anxiolytic³⁰ actions (binds to the “benzodiazapene receptor” portion of gamma-aminobutyric acid [a] receptors).

Much of the research on chrysin has been performed in vitro; this shows the potential for chrysin to inhibit the aromatase enzyme³¹ but human research has not shown that chrysin increases testosterone levels when used with androgen precursor molecules, such as androstenedione and DHEA.³² Chrysin is suspected of having low oral bioavailability; this flavone is thought to induce the very enzyme (UGT1A1) that hastens its own elimination in the intestine and liver.³³ Nonetheless, chrysin is widely used by athletes who tend to welcome any product with promise to enhance physical performance.

The end result of using aromatase inhibitors is to preserve testosterone by preventing its transformation into estrogens. Currently, three aromatase inhibitors are approved by the U.S. Food and Drug Administration: anastrozole (Arimidex[®]), exemestane (Aromasin[®]), and letrozole (Femara[®]) mainly for treating estrogen-dependent breast cancers when they first arise and when they recur.

Zinc

Zinc is a long-haired nutrient for prevention and treatment of men's health problems. Zinc is rather abundant in the body (totaling nearly 2 g) and is incorporated into many different enzyme systems in the body, underlying this mineral's importance in overall health. More specifically, suboptimal volumes of zinc appear to have a negative influence on serum testosterone concentrations as well as on seminal volume.³⁴

Not necessarily specific to andropause, zinc concentrations in the semen are directly correlated with sperm numbers.³⁵ Because of the large amount of zinc that is stored in the prostate gland and the relationship between prostate tissue levels and benign prostatic hyperplasia,³⁶ this mineral is lionized among people who use nutritional treatment to address prostate diseases. Zinc is also thought to serve as an inhibitor of 5-alpha reductase, the enzyme that converts testosterone to DHT.³⁷

Other Botanical Medicines

Puncture Vine

Tribulus terrestris, commonly known as puncture vine, has been used historically as a "tonic" herb for treating impotence. *Tribulus* is thought to increase testosterone levels indirectly by raising LH levels that come from the pituitary gland; the active component of *tribulus* is thought to be a type of saponin.³⁸

Specific research on *tribulus* in relation to its ability to elevate androgen levels is minimal. One experiment compared the sexual behavior of castrated laboratory animals that were untreated to those treated with either testosterone or *tribulus* extract. The researchers noted that, in both testosterone- and *tribulus*-treated groups, indicators of androgen activity were evident. These included increased prostate weight and measures of intracavernous pressure (degree of erection). The investigators concluded that the herb does have the ability to increase androgens (although measurement of actual levels was not performed).³⁹

The reputation of this herb (evidenced by historical use as an elevator of energy and vitality in indigenous medical systems) greatly precedes medical evidence. While the herb has promise as a promoter of libido and possibly androgen levels, more research is needed on its effects.

Potency Wood

Muirira puama, also known as "potency wood," is derived from the Brazilian Amazon and other parts of the Amazon rainforest. Long used by the indigenous people of South America, *muirira* has a reputation for treating sexual debility and baldness, among other conditions. Still highly valued in the Brazilian Pharmacopoeia (included since the 1950s), the herb is considered to be a powerful aphrodisiac. Active constituents are thought to include fatty acids, sesquiterpenes, monoterpenes, and alkaloids.⁴⁰

Relatively few clinical trials exist on the action of this herb, especially those that may be applicable to andropausal symptoms. One trial investigated the herb's effects in men who were experiencing decreased libido and impotence. The researchers found that 62 percent of subjects who took the herb in supplement form reported positive results in regard to libido, while 51 percent of those with erectile dysfunction felt that the herb was helpful.⁴¹

A second trial involving men with decreased libido used 1.5 g of *Muirira puama* extract per day; according to the investigators 85 percent of test subjects experienced enhanced libido, 90 percent experienced improved ability to maintain an erection, while 100 percent of subjects experienced an increase in frequency of intercourse.⁴² This herb appears to display possible benefits for the andropausal man in regard to improving sexual performance; more studies are needed to discern the mechanism by which this occurs.

Conclusions

Andropause, although more subtle than menopause, can be addressed in a number of ways, including hormone replacement, exercise, or supplementation. It is vital to individualize treatment after a careful examination and testing to rule out confounding factors. □

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