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This activity is designed for urologists who treat patients with sexual desire and arousal disorders, particularly erectile dysfunction. After participating in this activity, the participant should be able to:

- Recognize the special needs of various patient subtypes (eg, patients with chronic diseases, the elderly, and persons taking medications with sexual side effects).
- Describe the role of testosterone in maintaining normal genital structure and function; and identify and minimize the impact of chronic conditions and medications on testosterone level.
- List resources that may enhance patient education, staff development, and effective practice management.

#### CME Information

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Length of Time to Complete the Activity: 1 hour

#### Disclosure Information

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## The Link Between Sexual Dysfunction (Desire & Arousal Disorders) and Hypogonadism: Focus on Special Populations

Sexual feelings and response require not only healthy psychology, blood flow, and nerve function, but hormonal function as well. The role of androgens in sexual function and the links between chronic diseases and hypogonadism are poorly understood and generally underappreciated by most clinicians. I encourage you to pay attention to this emerging area of research because evidence accumulating from preclinical and clinical trials indicates that androgens are critical for sexual desire, arousal, and orgasm in both men and women. Yet, hypogonadism is a common problem, affecting an estimated 4 to 5 million men in the United States.<sup>1</sup> Aging and chronic diseases, such as diabetes, psychiatric disorders, rheumatoid arthritis, hypertension, multiple sclerosis, and many others, are some of the factors that have a negative effect on testosterone levels. This underrecognized problem deserves more attention, particularly in men with sexual dysfunction, since after correction of the hormonal milieu, the patient with hypogonadism may experience improved sexual function, including enhanced desire and erection in addition to improvements in ejaculation and orgasm.

### The Importance of Androgens in Normal Sexual Function

*What is most important for me to teach physicians about androgens and their role in sexual function?* It is important for physicians to recognize that androgens are necessary for healthy genital structure and function. Few people realize that androgen exposure is needed to maintain nerves, arteries, smooth muscles, and connective tissue in the genitals in both genders.

For example, Aversa et al<sup>2</sup> showed that patients with organic erectile dysfunction had free testosterone levels about 40% lower than patients with psychogenic erectile dysfunction. Free testosterone levels correlated with impaired compliance of cavernous arteries on dynamic duplex ultrasound. Moreover, in another investigation, androgen deficiency was shown to decrease the frequency of sexual desire, fantasy, and intercourse.<sup>3</sup> In eugonadal men, administration of exogenous testosterone may augment libido and the frequency and rigidity of spontaneous erections but does not necessarily stimulate sexual activity.<sup>4,5</sup> These studies support the role of testosterone in key domains related to sexual functioning—cognitive, affective, and physical.

It is also helpful for physicians to understand how sex hormones are produced (Figure 1) and how they function in the body. Sex hormones are continually produced since the body lacks

a means of storing them. They are synthesized from cholesterol primarily in the gonads and the adrenal glands and are also synthesized from dehydroepiandrosterone in other tissues, such as skin, muscle, bone, liver, and spleen. The enzyme desmolase removes six carbons from cholesterol, a 27-carbon structure, converting it into the 21-carbon pregnenolone. Pregnenolone is responsible for production not only of sex steroids, but also of mineralocorticoids involved in salt and water regulation, and of cortisol, which breaks down glycogen in the liver and, in conjunction with adrenaline, produces extra energy in response to stress. The mineralocorticoid and cortisol pathways are active throughout life.

In contrast, the pathway responsible for producing sex steroids does not become active until adrenarche or puberty. Genital tissue is not especially sensitive from birth through about the first 6 years of life. Between the ages of 8 and 10 years, the brain releases a factor, possibly corticotropin-releasing factor, that activates the enzyme 17,20-lyase. This enzyme triggers activity in the zona reticularis of the adrenal glands, where it converts hydroxypregnenolone to sex steroids, including 19-carbon androgens (dehydroepiandrosterone [DHEA], D5-androstenediol, androsterone, D5-androstenediol, D4-androstenedione, testosterone, dihydrotestosterone) and 18-carbon estrogens (estradiol, estrone, estriol).

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Free (ie, unbound, bioavailable) sex steroids then enter the cytoplasm of cells in the genitals. For example, testosterone enters smooth muscle cells in the corpus cavernosum of the penis where it binds to androgen receptors. The testosterone-receptor complex subsequently enters the cell nucleus where it scans androgen-sensitive parts of the genome and initiates genetic transcription and production of proteins, such as vascular endothelial growth factor, nerve growth factor, smooth muscle growth factor, endothelial growth factor, and other factors. These factors result in development and sensitization of genital tissue, promote body hair growth, and stimulate sexual thoughts and fantasies.

## Androgen Deficiency in Special Patient Populations

**Which of my male patients are most at risk of hypogonadism? Are there any “red flags” that should prompt me to ask about sexual function?** There are a number of risk factors for hypogonadism that are important for clinicians to recognize. Chronic conditions, such as diabetes, arthritis, fibromyalgia, chronic fatigue, psychiatric disorders, Parkinson’s disease, HIV infection, and multiple sclerosis—to name only a few—are associated with elevated levels of sex-hormone binding globulin (SHBG). SHBG and other binding proteins (eg, albumin) bind circulating sex hormones, preventing them from being taken up or utilized by tissues. Without continued exposure to active androgens and the growth factors they produce, persons with high SHBG levels return to almost a prepubertal state: genital tissue becomes less sensate and sexual desire and arousal are diminished.

Increased SHBG levels are also associated with normal aging and with certain hormone-altering drugs. As men age, DHEA, pregnenolone, androstenedione, and testosterone levels decrease and SHBG levels rise. In fact, it has been estimated that more than 60% of men over age 65 years have free testosterone levels below the normal values of men aged 30 to 35 years.<sup>1</sup> Leuprolide, which is used to suppress androgens in the treatment of prostate cancer, also has adverse effects on sexual desire and arousal. Other medications that can adversely affect androgen levels include antiepileptic drugs, digoxin, histidine H2-receptor antagonists, and clofibrate.

**Should I be concerned about these effects in my female patients too?** Yes, because the same types of chronic conditions and medications lower androgen levels in women just as they do in men. In addition, women

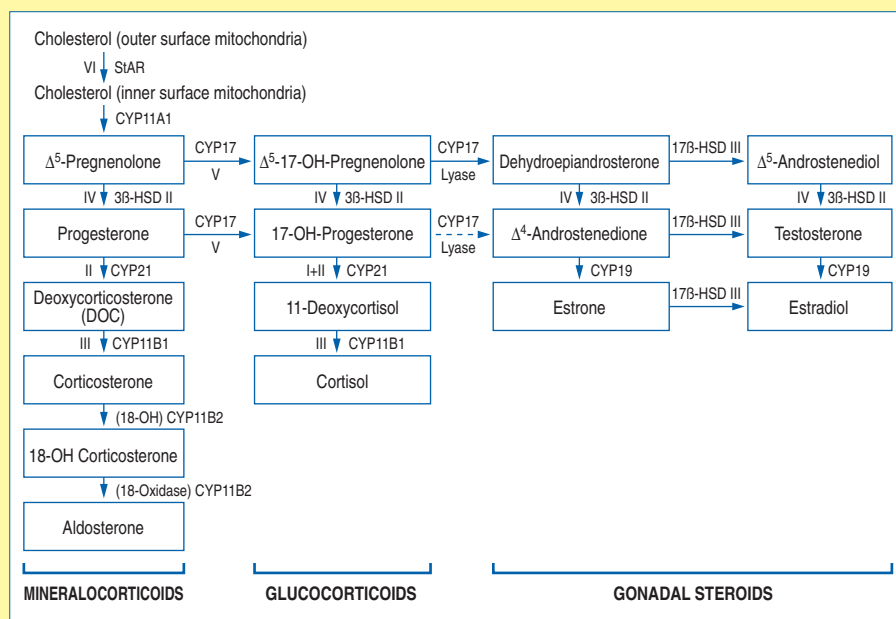


Figure 1: Hormone Biosynthesis.

taking oral contraceptives (OCs) have particularly low levels of free testosterone. This occurs because OCs elevate SHBG levels while concurrently suppressing ovarian production of androgens during three quarters of each cycle. Thus, as in persons with chronic conditions that raise SHBG levels, women taking OCs commonly develop diminished sexual desire and arousal responses. Similar effects occur in women who have undergone a hysterectomy/oophorectomy; those treated with leuprolide for management of endometriosis, infertility, or thyroid growth; or women taking tamoxifen for treatment or prevention of breast cancer. As in men, aging also results in decreased androgen levels in women, such that women in their 40s have about half the circulating testosterone level of women in their 20s.<sup>6</sup>

## Assessment for Hypogonadism

**If a patient with one of the risk factors described above complains about lack of sexual feelings, what further evaluation should I perform?** Androgen levels should be measured in patients with complaints of low arousal or sexual desire/interest, particularly if comorbid conditions are present. Other complaints common among patients with hypogonadism include decreased ejaculatory force, erectile function, and orgasm intensity. Note that measurement of total testosterone alone is insufficient to recognize androgen deficiency. Total serum testosterone includes

both bioavailable (free) and inactive (bound) testosterone and is, therefore, not a good indicator of active testosterone levels. Thus, when you evaluate a patient for hypogonadism, be sure to include not only total testosterone, but also free testosterone and SHBG values. Free testosterone = total testosterone/SHBG. Therefore, when the SHBG value is elevated, as it commonly is in persons with chronic medical conditions, the total testosterone value has to be supplemented to values above physiologically normal levels in order to achieve a normal free (or bioavailable) testosterone level.

Many physicians also fail to realize that androgen levels at the low end of normal may not correlate with normal physiologic sexual responsiveness. This occurs because laboratory definitions of normal androgen levels are based on healthy population samples that still include persons with desire and arousal or other sexual disorders. Since 43% of women and 31% of men who are otherwise healthy have some type of sexual dysfunction,<sup>7</sup> inclusion of this subgroup has a tremendous influence on perceived normal values. As a result, the reported normal androgen range is probably inappropriately wide. In a recent study we conducted,<sup>8</sup> we measured testosterone levels in persons who were healthy and had good sexual function and found much higher testosterone levels than are commonly considered normal. In fact, our results suggest that the lower third of what is usually considered normal is actually abnormally low testosterone.

## Treatment for Hypogonadism

### *Do patients with chronic medical conditions generally accept the addition of treatment for hypogonadism to their management plan?*

Patients with chronic disease often face complicated medical management issues in their overall care. In contrast, testosterone supplementation may be considered simple and safe, and should certainly be considered for those with evidence of hypogonadism. Testosterone supplementation is available in injection, topical gel, transdermal patch, or buccal mucoadhesive tablet formulations, the advantages and disadvantages of which I described in the previous issue of this *Expert Insights* series.

Numerous studies have confirmed the efficacy of testosterone supplementation in improving sexual function in both men and women with low androgen levels. A meta-analysis of 73 studies of testosterone supplementation for erectile dysfunction reported overall response rate of 57% (7% with placebo).<sup>9</sup> In a randomized, placebo-controlled crossover study of premenopausal women with low libido and testosterone level, testosterone therapy improved well-being, mood, and sexual function.<sup>6</sup>

There are also studies to support testosterone supplementation in special populations. In men with type 2 diabetes, visceral obesity, and evidence of androgen deficiency, testosterone supplementation improved glucose homeostasis, body composition,

and symptoms of hypogonadism, including erectile dysfunction, compared with patients who received no treatment.<sup>10</sup> Testosterone injections improved libido in 74% of men with hypogonadal symptoms and symptomatic HIV infection. In this population, it also increased energy in 59% of those with fatigue, improved mood in 58% of those with an Axis I depressive disorder at baseline, and resulted in average muscle mass increase of 1.6 kg for the whole group and 2.2 kg for those with wasting at baseline.<sup>11</sup>

DHEA and androstenedione supplements are also commercially available without a prescription, usually through health food stores. Double-blind, placebo-controlled trials have shown improved sexual response in men taking DHEA.<sup>12</sup> However, caution is advised when taking or recommending such products, since they are unregulated by the FDA. Product contents often vary considerably from what is stated on the package labeling.

Androgen therapy is contraindicated in men with prostate cancer and women with breast cancer or who are pregnant. Once androgen therapy is initiated, quarterly follow-up should include assessment of clinical changes as well as biochemical analyses of androgen, estrogen, SHBG, luteinizing hormone, follicle-stimulating hormone, prolactin, complete blood cell count, liver function tests, and lipids, and the dose should be adjusted accordingly.

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## Tips & Resources

### Tips for Patients

Institute for Sexual Medicine, Boston University School of Medicine: Sexual medicine information sessions and online information for patients. For information, [www.bumc.bu.edu/sexualmedicine](http://www.bumc.bu.edu/sexualmedicine)

Erectile Dysfunction Institute: Information and support for patients with erectile dysfunction and prostate cancer; toll-free nurse line: [www.erectile-dysfunction-impotence.org/Impotence-Causes/Prostate-Cancer-Treatment.html](http://www.erectile-dysfunction-impotence.org/Impotence-Causes/Prostate-Cancer-Treatment.html)

Joslin Diabetes Center: Patient information on sexual dysfunction and diabetes, including treatment options and a sexual dysfunction quiz specifically designed for men and women. For information, [www.joslin.harvard.edu/education/library/sexual\\_dysfunction.shtml](http://www.joslin.harvard.edu/education/library/sexual_dysfunction.shtml)

Sexual Health Network: Information and support regarding sexuality for individuals with disabilities, illnesses, or life cycle changes. For information, [www.sexualhealth.com/](http://www.sexualhealth.com/)

### News and Notes

Society for Sex Therapy and Research Annual Meeting, April 1-4, 2004, Arlington, Va. For information, [www.sstarnet.org/](http://www.sstarnet.org/) or call 202-863-1648.

American Association of Sex Educators, Counselors and Therapists Meeting, May 12-16, 2004, Chicago, Ill. For information, [www.aasect.org/](http://www.aasect.org/) or call 804-644-3288.

Free public seminars presented by Irwin Goldstein, MD, at the Holiday Inn, Newton, Mass. "Female Sexual Dysfunction: Symptoms and Solutions," May 23, 2004; and "Sexual Dysfunctions in Men: Symptoms and Solutions," June 6, 2004. For information and online registration, [www.bumc.bu.edu/sexualmedicine/msdseminar/](http://www.bumc.bu.edu/sexualmedicine/msdseminar/) or call 617-638-8576.

### Recent Publications

A comprehensive retrospective review of 72 studies found no causal relationship between testosterone replacement and prostate cancer or heart disease risk. In addition, this study described other potential side effects of testosterone replacement therapy as infrequent (acne, sleep apnea), rarely of clinical significance (fluid retention), or reversible with cessation of treatment (gynecomastia, testicular atrophy, infertility).

Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. *N Engl J Med*. 2004;350:482-492.



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## Case Vignettes

*A patient with rheumatoid arthritis presented with complaints of erectile dysfunction and low sexual interest. He has had only modest success with PDE5 inhibitors. What should I do next?*

As discussed in this issue of *Expert Insights*, patients with chronic illnesses commonly develop hypogonadism, which can contribute to poor sexual functioning. For example, I have a 54-year-old patient with diabetes who is also a heavy smoker and drinker. At his wife's urging, he presented for treatment of erectile dysfunction and requested vardenafil, which he had seen on a televised commercial during a football game. After receiving education about the need for modification of contributing lifestyle factors (ie, his drinking, smoking, and glucose control), he was treated as requested but reported only moderate improvement. Hormonal evaluation revealed low free and total testosterone and low DHEA. He continued on vardenafil with the addition of testosterone gel and DHEA supplementation. After a few months, he reported not only improved sexual function but an increase in energy. He had begun exercising at a gym, lost weight and had also stopped smoking. Subsequent hormone measurements indicated a eugonadal state.

*In a patient with multiple sclerosis, is sexual dysfunction always attributable to nerve damage?*

No, in fact, I had a patient with a similar condition, transverse myelitis, and associated lower extremity weakness requiring him to use a cane in order to walk. He reported a muted orgasm and a "numbing" of sensation in his penis. His primary care physician and neurologist had attributed these problems to the transverse myelitis and advised him that nothing could be done. However, recent data on the function of androgens has shown that the dorsal nerve of the penis, which provides afferent sensory information to the brain, is an androgen-dependent nerve responsible for orgasm. Low androgen levels can affect this nerve and can also cause genital numbness. Hormonal evaluation of this patient confirmed low androgen levels, which were reversed

with testosterone supplementation. Treatment successfully restored sexual sensation and orgasmic intensity.

*Is loss of sexual desire a common and long-term consequence of grief from losing one's spouse? Should anything be done to intervene in this apparent grief response?*

The clinical description of widower's syndrome involves a man no longer interested in sex because his wife is deceased. Although this scenario is common, it is not necessarily a long-term, asexual lifestyle for grieving widowers.

A gentleman came to see me two years after losing his wife of 25 years to breast cancer. He had met a woman several months before and developed a warm and close relationship with her. The woman wanted to take the relationship to the next level, a committed and sexual level. In contrast, he had no interest in a sexual relationship. At the woman's insistence, he tried sex therapy and counseling but to no avail. In my office he completed several intake questionnaires, including the Androgen Deficiency in the Aging Male (ADAM) questionnaire. Results of the ADAM questionnaire were suspicious of a diagnosis of androgen insufficiency, and a follow-up battery of androgen tests confirmed a hypogonadal state. He recognized that he wanted to be with this woman, but his body was not interested in hers—his penis was not responding; it felt "like a flat tire." He was started on a testosterone gel, and he began having morning erections and sexual thoughts and fantasies that he had not experienced in a while. When I measured his blood counts after 3 months, they were physiologically normal. The two of them had been going to couples therapy throughout this time and continued for another 3 months. Within 6 months, he felt less depressed, had more energy, and was able to stay awake after meals. His penis felt more sensitive, and he was able to ejaculate and have orgasms which he had not been able to do even while attempting masturbation to "check if his equipment worked." He became interested in a sexual relationship with this woman that resulted in his wanting to commit to her. What had been thought to be a pure grief reaction was, in part, a hypogonadal state.

## Put It Into Practice

- Sexual health deserves attention by physicians treating special populations, such as patients with chronic illnesses or those taking medications associated with diminished sexual function.
- Questions about libido and sexual function can help elicit concerns that patients may otherwise be embarrassed to raise.
- Androgen levels, including total and free testosterone and SHBG, should be evaluated in patients with low desire/arousal.
- Modification of the hormonal milieu with topical testosterone supplementation is easy and safe and has a large impact on genital structure and function in patients with low or low-normal levels.

## Issues In This Series

Issue 1: Focus on Epidemiology and Etiology

Issue 2: Focus on Clinical Evaluation

Issue 3: Focus on Treatment

Issue 4: Focus on Special Populations

Issue 5: Focus on Psychosocial Aspects

Issue 6: Focus on Optimizing Outcomes

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