Testosterone and Erectile Function: An Unresolved Enigma

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Erectile function depends on a complex interrelationship between psychological, neurologic, vascular, and endocrine factors. It is well known that androgens play a critical role in the physiology of erectile function. This statement was based on several clinical observations: (1) castration is associated with a decline in sexual interest and erectile function, although some potency may be maintained; (2) antiandrogens result in erectile dysfunction (ED), although sexual interest may persist; and (3) androgen supplementation improves sexual function in hypogonadal men. However, the underlying mechanisms by which androgens regulate erectile function are poorly defined [1]. In their in depth and thoughtful review article, Traish et al provide an extensive analysis of the cellular, molecular, and physiologic mechanisms of androgens in erectile physiology and try to incorporate current evidence into clinical practice [2]. Several questions are raised from this article that stimulate discussion and provide guidance for future research.

1. Do we have hard data that androgens are critical for erectile function?

Preclinical studies provide evidence that androgens modulate erectile function in several ways [1]. Testosterone may regulate central and peripheral mechanisms of penile erection. Androgen deficiency is associated with structural changes in the cavernous nerves consistent with nerve atrophy and androgen supplementation may reverse these changes resulting in nerve regeneration. Although these data remain to be proved in humans, they may explain the lack of clinical response with androgen therapy in men. The expression and activity of nitrous oxide synthase (NOS) isoforms in the corpus cavernosum is reduced after castration and these changes are reversed with androgen administration. Because smooth muscle relaxation and erection depend on NO, they are believed to be androgen dependent too. Furthermore, castration has been shown to reduce the expression and activity of phosphodiesterase type 5 (PDE5) and androgen supplementation has been shown to up-regulate the expression and activity of PDE5. These data are consistent with the clinical evidence that although PDE5 administration may improve erectile function in hypogonadal men or men with low testosterone levels, erectile response is maximized following androgen supplementation. Finally, androgen deprivation significantly reduces trabecular smooth muscle content and increases connective tissue deposition. Furthermore, smooth muscle appears disorganized, with a large number of cytoplasmic vacuoles, whereas cellular structures resembling adipocytes have been identified in the subtunical region of the corpus cavernosum. These observations are also consistent with basic research and clinical/pathologic evidence showing that reduced cavernosal smooth muscle content is associated with venoocclusive dysfunction. Although most data are based on animal studies that cannot be extrapolated to
Humans, a growing body of evidence supports the important role of androgens in erectile function.

In humans, androgens are critical for the development and growth of secondary sexual organs including the penis. Children with androgen deficiency develop micropenis, whereas this is not the case after attainment of sexual maturity. Androgen ablation in patients with prostate cancer significantly reduces frequency, duration, and rigidity of nocturnal erections based on nocturnal penis tumescence and rigidity (NPTR) recordings. Furthermore, erectile function domain scores on the International Index of Erectile Function (IIEF) are reduced in hypogonadal men, whereas testosterone administration is able to reverse the abnormal NPTR recordings and improve erectile function. The high prevalence of hypogonadism and ED in metabolic syndrome and its components is another field of current research [3]. Low testosterone is strongly associated with the metabolic syndrome and ED is highly associated with the metabolic syndrome and comorbidities associated with it; hypogonadism is a predictor of type 2 diabetes and androgen-deprivation therapy for prostate cancer is associated with increased risk of diabetes, coronary heart disease, myocardial infarction, sudden cardiac death, and worsening of existing diabetes. Besides that, testosterone therapy may improve insulin sensitivity and reduce abdominal obesity. However, it remains unclear whether hypogonadism contributes to the pathogenesis of the metabolic syndrome or the reverse is true.

2. Which is the appropriate work-up in hypogonadal men with ED?

Prevalence rates of androgen insufficiency and ED vary from 1.7% to 35% in different studies, depending on the study sample and setting. Late-onset hypogonadism (LOH) is a clinical and biochemical syndrome frequently associated with advancing age and characterized by a deficiency in serum androgen levels, with or without changes in receptor sensitivity to androgens. It may affect the function of multiple organ systems and result in significant detriment in the quality of life, including major alterations in sexual function. Sexual dysfunction may be the presenting symptom but depression, irritability, cognition and sleep disturbances, increase in visceral fat, decrease in body hair, and skin alterations must not be neglected in history-taking and clinical assessment. Biochemical determination of low androgen levels must accompany clinical evidence for androgen insufficiency.

Medical and sexual history, incorporating physical examination findings, will usually reveal suspicious cases of hypogonadism. Screening questionnaires (Androgen Deficiency in the Aging Male [ADAM], Aging Males Symptoms, [AMS] and a structured interview [ANDROTEST]) are relatively nonspecific and they are not recommended in clinical practice [4]. Testosterone assessment remains a major point of debate. Total testosterone values follow the circadian rhythm and measurement in the early morning is recommended, despite the fact that this circadian rhythm is lost with aging and morning assessment may not be as important as it was thought to be. But should we measure total testosterone? Due to the fact that only unbound testosterone is active and sex hormone-binding globulin (SHBG) is increasing with age, total testosterone assessment is considered today unreliable. Bioavailable and free testosterone assessments are recommended. Although measurement of bioavailable testosterone is reliable, this is not the case for free testosterone. Therefore, the most accessible and reliable assays to establish the presence of hypogonadism are the measurement of bioavailable testosterone or the calculated free testosterone (cFT). This assessment is incorporated in basic evaluation of the patient with ED in almost all current guidelines [5,6].

3. Why is erectile function preserved in some men with low androgen levels?

It seems that there is a testosterone threshold value (about 10% of the normal values), below which erectile function declines in a dose-dependent fashion [7]. Androgen-dependent tissues have varying sensitivities to circulating testosterone levels. Androgen receptor polymorphism may play a key role. This means that an individual with low testosterone values may maintain erections due to the high activity of androgen receptor and vice versa. In addition, testosterone is not the only androgen associated with erectile function but dihydrotestosterone (DHT), adrenal androgens (such as dehydroepiandrosterone [DHEA] and DHEA sulfate [DHEA-S]), estrogens, and conjugated metabolites are also important. Should we measure all these hormones? The answer is no for the routine clinical practice, but in some specific cases this assessment may be of value although these determinations are complex and not yet standardized. These may include patients treated with 5α-reductase inhibitors or those for whom there is no clear reason for the lack of response to testosterone. Similarly, “traditional” hormonal assessment including follicle-stimulating
hormone (FSH), luteinizing hormone (LH), thyroid-stimulating hormone (TSH), and prolactin is not indicated in the uncomplicated evaluation of ED associated with LOH, but must considered when systemic endocrine disorders are suspected or when androgen supplementation fails to restore hypogonadism and erectile function.

4. **How should we treat the hypogonadal man with ED?**

Although several testosterone formulations are available, testosterone topical gel and long-term depot injections are the preferred treatment options today, due to their favorite pharmacokinetic profile characterized by relatively constant plasma levels, avoiding wide fluctuations and minimal side effects. A point of debate is the presence of borderline testosterone levels. Testosterone supplementation in these patients is generally justified especially in those not responding to PDE5 inhibitors (PDE5-Is). The therapeutic role of other treatments (such as DHEA, aromatase inhibitors, or clomiphene citrate) is not supported by rigorous data and may be considered only in selected cases with complex endocrine disorders. PDE5-Is are today the first treatment option for men with ED. Although as many as 75% of hypogonadal men with ED may respond to a PDE5-I alone, response is maximized after combination treatment [8]. Another point of interest is patients with borderline or abnormal testosterone levels do not respond to PDE5-Is; in such patients LOH may be the cause, and physicians should be aware that coadministration of testosterone supplementation with a PDE5-I may reverse non-responders to responders. Initial studies have shown that up to 58% of patients converted to responders with this combination treatment [9]. However, because several other risk factors for ED may be present in elderly men, testosterone supplementation may not restore erectile function despite normalization of testosterone levels.

Finally, attention should be paid to the follow-up protocol for patients receiving testosterone supplementation. Testosterone assessment, hematologic examinations (hematocrit and hemoglobin), liver function tests, bone density, and a lipid profile must be periodically evaluated although there is no consensus on optimal time intervals. Digital rectal examination (DRE) and determination of serum prostate-specific antigen (PSA) are mandatory in men over the age of 45 yr as baseline measurements of prostate health prior to therapy with testosterone, at quarterly intervals for the first 12 mo, and yearly thereafter. Although it is commonly believed that testosterone causes enhanced growth of prostate cancer, this association is poorly defined [10]. No large, long-term studies of testosterone replacement therapy have been performed. The prostate cancer rates in published studies are approximately 1%, similar to the cancer detection rate in prostate cancer screening trials. While we wait for large-scale, well-designed studies with high-level evidence, patients receiving testosterone replacement therapy need close medical monitoring.

**References**