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REVIEW

Translational Perspective on the Role of Testosterone in Sexual Function and Dysfunction

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ABSTRACT

Introduction: The biological importance of testosterone is generally accepted by the medical community; however, controversy focuses on its relevance to sexual function and the sexual response, and our understanding of the extent of its role in this area is evolving.

Aim: To provide scientific evidence examining the role of testosterone at the cellular and molecular levels as it pertains to normal erectile physiology and the development of erectile dysfunction and to assist in guiding successful therapeutic interventions for androgen-dependent sexual dysfunction.

Methods: In this White Paper, the Basic Science Committee of the Sexual Medicine Society of North America assessed the current basic science literature examining the role of testosterone in sexual function and dysfunction.

Results: Testosterone plays an important role in sexual function through multiple processes: physiologic (stimulates activity of nitric oxide synthase), developmental (establishes and maintains the structural and functional integrity of the penis), neural (development, maintenance, function, and plasticity of the cavernous nerve and pelvic ganglia), therapeutically for dysfunctional regulation (beneficial effect on aging, diabetes, and prostatectomy), and phosphodiesterase type 5 inhibition (testosterone supplement to counteract phosphodiesterase type 5 inhibitor resistance).

Conclusion: Despite controversies concerning testosterone with regard to sexual function, basic science studies provide incontrovertible evidence for a significant role of testosterone in sexual function and suggest that properly administered testosterone therapy is potentially advantageous for treating male sexual dysfunction.

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Key Words: Testosterone; Penis; Development; Morphology; Autonomic Input; Prostatectomy; Diabetes; Aging; Phosphodiesterase Type 5 Inhibitor

INTRODUCTION: ARTHUR L. BURNETT

Perhaps there is no other subject matter in sexual medicine today that garners as much attention, if not controversy, as testosterone. This commonly known "sex hormone" stirs interest because of its generally accepted importance in diverse aspects of male sexual prowess, although it also is associated with a plethora of other masculine characteristics. Relevant to this topic is the concept of "testosterone deficiency" or "androgen deficiency" in reference to a clinical entity of androgen-dependent biological dysfunctions including not just impaired sexual development and function but also impaired sense of well-being, sarcopenia, decreased strength, decreased bone mineral density, anemia, and cognitive dysfunction. Recognizable, too, is the phrase "testosterone replacement therapy," which denotes treatment for the condition of testosterone deficiency. These terms are pervasive in the lay and medical persons' lexicon, promoted by widespread mass media, and reflected by a worldwide commercial industry surge in testosterone products and their prescriptive use in recent years.[1,2]

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The controversy surrounding testosterone derives from several sources. The biological importance of this hormone in sexual function suffices as a matter of debate. Although testosterone is generally accepted by the medical community to be involved in the sexual response (male and possibly female), its role and extent of effects in this arena continue to be defined. The physiology of the sexual response conventionally focuses on the vascular and neurologic systems, and the endocrine system is often assigned a secondary biological role. This role should not go unnoticed, because testosterone might serve as an essential factor in sexual biologic function and act critically to modulate multiple molecular mechanisms related to this field of study. Ongoing scientific study can be expected to elucidate these roles.

The clinical management of "testosterone deficiency" has historically been controversial, and recent epidemiologic observations have fueled the tempest. Although testosterone products have been approved by regulatory bodies in the United States for more than 50 years and thus represent a known and accepted therapy in contemporary medical practice, concern exists that these products are being used inappropriately and possibly overused. Indications for testosterone replacement therapy appropriately specify the treatment of primary hypogonadism (testicular failure) and hypogonadotropic hypogonadism (congenital or acquired) in men, so it is applicable to men having confirmed signs and symptoms of testosterone deficiency.[3] Dissent arises when determining appropriate candidates for therapy. Older men are often recipients of therapy because of demonstrated testosterone deficiency in these men, which is consistent with a known decrease in serum testosterone levels at a rate of 1% annually after 40 years of age.[4] Arguable points are whether the hormone decline is a physiologic aspect of aging rather than a pathologic process and whether testosterone treatment is an enhancement rather than a necessary remedy of poor health. Men with adverse health conditions such as hypertension, hypercholesterolemia, and diabetes mellitus (DM) are recognized candidates for therapy based on evidence of decreased testosterone in men with these comorbidities.[5–8] In addition to adverse health and lifestyle considerations, emerging environmental factors causing impairments in hormone function also might be in play.[9] Accordingly, increased use of this therapy can be attributed at least in part to a host of adverse societal changes in addition to the fact that those affected by hypogonadism represent an expanding segment of the population.

With respect to the role of testosterone therapy in treating male sexual dysfunction specifically, the proven benefit of therapy has been questioned in the past, although recent literature is supportive in this regard. Historical studies showing benefit often were confounded by many limitations such as inclusion of trial enrollees without definite biochemical evidence of testosterone deficiency, inclusion of trial enrollees lacking baseline sexual dysfunction, use of non-validated sexual dysfunction outcome instruments, and weak study design overall. Rigorously performed meta-analytic studies have disputably supported the positive impact of testosterone therapy.[10,11] In one recent analysis comprising 29 randomized controlled trials, testosterone therapy was found to improve several aspects of male sexual function in confirmed testosterone-deficient patients such as erectile function, sexual desire, orgasmic function, and intercourse sexual satisfaction.[11] This level of evidence and ongoing appropriately designed studies lay the groundwork toward establishing that properly administered testosterone therapy benefits male sexual function.

Another concern surrounding testosterone therapy justly considers its possible health risks, prompting deliberation as to whether its harms outweigh its benefits.[12] Much of the concern pertains to potential cardiovascular morbidity and mortality arising from this therapy, stoked in part by recent publications investigating this possibility.[13,14] Longstanding reservations regarding other potential risks of therapy relating to prostate cancer, worsening lower urinary tract symptoms, worsening obstructive sleep apnea, and erythrocytosis also are frequently cited, although delineation of these risks await definitive clinical trials. Further investigation also is warranted to establish the scientific basis for real and theorized adverse clinical effects of this therapy, particularly in the long term.

Despite controversies surrounding testosterone, particularly with regard to sexual function, the incontrovertible current storyline is that the hormone is relevant for sexual function and its appropriate therapeutic administration is potentially advantageous for treating sexual dysfunction. Ongoing investigation is clearly needed in several areas of this subject to refine understanding as to the particular roles of this hormone and establish fully the indications, benefits, and risks of testosterone therapy. Scientific study at all levels of basic, clinical, translational, and population science is envisioned to contribute to advancing the field, offering to evince testosterone as an important factor in sexual function.

This White Paper was conceived after acknowledging that basic scientific evidence is relevant in establishing testosterone's influence on sexual function. The Basic Science Committee of the Sexual Medicine Society of North America was commissioned to produce a report examining this subject with the principal aim of providing a basic scientific evidence-based assessment of the role of testosterone in sexual function and dysfunction. This endeavor was aimed secondarily to inform the clinical management of testosterone deficiency in sexual medicine and assist in guiding successful therapeutic interventions associated with testosterone therapy for androgen-dependent sexual dysfunction. This report consists of sections covering select subject areas related to the main topic. A conclusion section serves to summarize and synthesize the content of information of the report followed by recommendations for conducting further basic scientific research in this field.

ROLE OF TESTOSTERONE IN CELLULAR PHYSIOLOGY: JOHN MUHALL, KELVIN DAVIES

Testosterone is widely accepted as playing a role in male sexual anatomy and function.[15,16] However, its physiologic role in human erectile function remains a matter of some controversy.[17–20] Studies in animals have provided strong evidence of a regulatory role for