Testosterone in Women: Measurement and Therapeutic Use

Ann Kathryn Korkidakis, MD; Robert L Reid, MD

Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynaecology, Queen's University, Kingston, ON

Abstract

Androgens, both in excessive and depleted states, have been implicated in female reproductive health disorders. As such, serum testosterone measurements are frequently ordered by physicians in cases of sexual dysfunction and in women presenting with hirsutism. Commercially available androgen assays have significant limitations in the female population. Furthermore, the measurements themselves are not always informative in patient diagnosis, treatment, or prognosis. This article reviews the limitations of serum androgen measurements in women suspected to have elevated or reduced androgen action. Finally, we consider when therapeutic use of androgen replacement may be appropriate for women with sexual interest/arousal disorders.

Résumé

Divers troubles de santé génésique chez la femme découlent d'un taux anormal d'androgènes. C'est pourquoi les médecins demandent souvent un dosage du taux sérique de testostérone chez les femmes atteintes d'hirsutisme ou souffrant de dysfonctionnement sexuel. L'efficacité des tests commerciaux de dosage des androgènes est toutefois limitée chez la femme, et les résultats ne permettent pas toujours de poser un diagnostic, de planifier un traitement ou de formuler un pronostic. Le présent article se penche sur les limites du dosage des androgènes chez les femmes semblant présenter une activité androgénique anormale et étudie les situations où une thérapie hormonale est appropriée chez les femmes atteintes d'un trouble de l'intérêt ou du désir sexuel.

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Corresponding Author: Dr. Ann Kathryn Korkidakis, Queen's University, Kingston, ON. 12akk1@queensu.ca

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ANDROGEN PHYSIOLOGY IN WOMEN

Androgens are synthesized in both the adrenals and the ovaries in response to adrenocorticotropic hormone and luteinizing hormone, respectively. These steroids are also derived from conversion of precursors in peripheral tissues. Until recently the major androgens in the female circulation were believed to be dehydroepiandrosterone, androstenedione, and testosterone.[1]

The most potent androgens are produced in peripheral sites (skin, pilosebaceous unit, and adipose tissue) where the enzyme 5a-reductase acts on steroids arriving via the circulation. Until recently the most significant peripherally derived androgen has been believed to be dihydrotestosterone. Another adrenal steroid, 11β-hydroxyandrostenedione, has for a long time been written off as a by-product of adrenal steroid metabolism and, as such, was seldom even included in the adrenal steroidogenic pathway. Recent studies, however, have revealed that 11β-hydroxyandrostenedione is not a dead-end product of steroidogenesis. This C19 steroid serves as the precursor to the androgenic steroid 11 ketotestosterone.[2] When acted upon by 5a-reductase in peripheral tissues, 11 ketotestosterone is converted to 11-ketodihydrotestosterone, which exerts a local effect on androgen receptors comparable with DHT.[3]

The majority of circulating testosterone is bound to sex hormone–binding globulin (66%) and with lower affinity to albumin (33%). The remaining 1% to 2% of testosterone is in a free, unbound state ("free testosterone"). The combination of free testosterone and albumin-bound testosterone is also referred to as the "bioavailable" forms of testosterone.[4] In females, this bioavailable testosterone is found in nanomolar to micromolar concentrations.[4] Significant androgen action results from the peripheral synthesis of DHT and 11KDHT, which have minimal release into the circulation.[2]

In premenopausal women, circulating testosterone levels fluctuate during the menstrual cycle, with a peak occurring midcycle. There is also diurnal cyclicity, with rising levels in

the early morning.[3] In this population, approximately 25% of circulating testosterone is derived from the ovaries, 25% from the adrenals, and the remaining from peripheral tissue.[3]

Most of the circulating androgens after menopause are of adrenal origin.[5] It is difficult to disentangle the effects of aging and the impact of menopause on circulating androgen levels. Total and free testosterone, androstenedione, and dehydroepiandrosterone all show the most pronounced decline between ages 20 and 45. Androgen levels continue to decline at a slower rate with advancing age and reach a nadir in the early to mid-60s for total and free testosterone, around 70 years for androstenedione, and in the mid- to late 70s for DHEAS.[6] In menopause and following oophorectomy, circulating testosterone levels are 50% lower than in the early reproductive years.[6]

LIMITATIONS OF ANDROGEN ASSAYS

Immunoassays measuring plasma androgens in women have notable limitations. Importantly, these tests were initially developed to measure androgen levels in men, and their sensitivity is compromised when concentrations are as low as those found in the female population.[7] Additionally, these molecules have very similar configurations to other steroids, rendering it difficult to obtain an accurate level of the hormone in question.[8]

There is considerable debate regarding what measurement is most reflective of testosterone activity.[8,9] Free testosterone is commonly used because it appears to be a better marker of androgenicity than is total testosterone.[10] It is reasonable, however, to also include the portion of testosterone that is bound to albumin. Albumin has a low affinity for testosterone, rendering the hormone available for biologic action.[4]

Classically, steroid hormones have been measured through radioimmunoassays. This methodology was first described in 1969. Using radiolabeled monoclonal antibodies, testosterone can be extracted and then purified. Given that protein-bound steroids are eliminated, only free testosterone levels can be measured with this technique. This process is technically simple and rapid; however, accuracy at testosterone levels <300 ng/dL is limited.[11]

More recently, gas/liquid chromatography—mass spectrometry and equilibrium dialysis assays have been developed.[12] These techniques produce highly accurate measurements at a faster pace. The necessary instrumentation, however, is very costly and requires highly trained technicians. As such, this technology is generally not available in non-tertiary centres.[13]

Non-extraction radioimmunoassays have been developed for commercial use and are currently widely used in laboratories.[14] These "direct" assays bypass the steroid purification step, which simplifies and hastens sample processing. Their sensitivities and inter-assay comparability are, however, limited. Importantly, laboratories often do not validate the assays performed with reagents from these commercial kits. Furthermore, these testosterone assays have been shown to be unreliable in the female population.[15] In fact, in reference to one study analyzing direct immunoassay kits in the female population, the editors commented that "guessing appears to be nearly as good as most commercially available immunoassays and clearly superior to some."[16]

Current methods estimate only serologic levels and do not account for the aforementioned proportion of intracellular testosterone known to exert physiologic action.[17] The known diurnal and menstrual cyclicity of testosterone levels adds further complexity in obtaining and interpreting assay values.[4]

Given that there is no standardized testosterone assay with established gender and age-based normative values, it follows that measurement of androgens in most clinical situations will afford little insight into diagnosis or treatment. Collaborative efforts are being undertaken to provide accuracy-based, calibrated testosterone testing and to define appropriate reference intervals.[11]

ROLE OF ANDROGEN MEASUREMENTS IN THE ASSESSMENT OF FEMALE SEXUAL INTEREST/ AROUSAL DISORDER

Female sexual dysfunction is a complex, heterogeneous phenomenon. As such, the classification of these disorders is in constant evolution. Recently, the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* merged "hypoactive sexual desire disorder" and "female sexual arousal disorder" into a single diagnosis of "female

ABBREVIATIONS

11KDHT	11-ketodihydrotestosterone
DHEAS	dehydroepiandrosterone
DHT	dihydrotestosterone
PCOS	polycystic ovary syndrome
SSE	satisfying sexual episode