Editorial: Female Androgen Deficiency Syndrome—An Unproven Hypothesis

In this issue of the JCEM, Santoro et al. (1) describe the correlates of circulating androgen levels in midlife women. The data from this important Study of Women’s Health Across the Nation (SWAN) demonstrate only a weak association of testosterone levels with sexual desire, sexual arousal, and well-being—symptoms that have been commonly attributed to androgen deficiency in women. These data raise further questions about the concept of a female deficiency syndrome, a timely topic that has witnessed considerable media attention and controversy after the Federal Drug Administration’s disapproval of the female testosterone patch.

There are several reasons why this topic has continued to be controversial. First, there has been a striking lack of consensus on how to define androgen deficiency quantitatively in women. The problems with RIAs for the measurement of serum testosterone levels, a crucial marker of androgen deficiency, have eroded credibility of the entire field. Only limited normative data for healthy menstruating women in different phases of the menstrual cycles are available from research laboratories (2–4), where they have been derived generally from small convenience samples. The paucity of normative data and insufficient precision and accuracy of commercially available testosterone RIAs in the low range prevalent in women (5) have made it difficult to establish thresholds for defining androgen deficiency in women. Indeed, it is possible that local androgen metabolism might play an important role in mediating testosterone’s tissue-specific effects (6). In addition, there is poor understanding of how pulsatile, diurnal, and circannual rhythms in testosterone secretion and variation across different phases of the menstrual cycle in women impact on interpretation of randomly obtained testosterone levels in women.

Serum total testosterone concentrations, representing the sum of the unbound and protein-bound testosterone in circulation, have been measured for the past 30 yr by RIAs or immunometric assays. Historically, assays for the measurement of serum testosterone levels employed extraction using organic solvents, chromatography to separate testosterone from other potentially cross-reacting steroids, followed by RIA. With the availability of more specific antibodies, the extraction and chromatography steps were eliminated in most commercial and in many research laboratories. In a comparison of several commercial RIAs against liquid chromatography, tandem mass spectrometry (LC-MS/MS), Wang et al. (5) reported that many widely used commercial testosterone assays lacked accuracy in the low range (<100 ng/dl) (5, 7). Furthermore, the normative ranges vary for different testosterone RIAs.

Although some research laboratories have gone to great lengths (LC-MS/MS) to validate testosterone RIAs in the low range, these research assays are not available readily to clinical practitioners. LC-MS/MS, the gold standard for the measurement of testosterone levels, has become available in some commercial and research laboratories. This technique has the desired sensitivity and accuracy in the low range, but its use is limited by its high cost and paucity of normative data. Decisions about assay selection should take into account accuracy, sensitivity, cost, and analytical time.

Measurement of free or unbound testosterone, which represents only 0.5–3% of circulating testosterone in women, is also problematic. Most circulating testosterone is bound to SHBG and albumin. The free fraction can be measured by equilibrium dialysis, which is still considered the gold standard for the measurement of free testosterone. The term “bioavailable testosterone” refers to unbound testosterone plus testosterone bound loosely to albumin, and reflects the view that, in addition to the unbound testosterone, albumin-bound testosterone is readily dissociable and thus bioavailable at the tissue level. Bioavailable testosterone levels, measured by the ammonium sulfate precipitation method, have been shown to correlate well with the clinical state, but these methods are not available readily in many hospital laboratories. Free and bioavailable testosterone concentrations can also be calculated from total testosterone and SHBG concentrations using published algorithms. Tracer analog methods are relatively inexpensive and convenient, but they are affected by SHBG concentrations (8) and can therefore be inaccurate in providing a true index of “free” testosterone.

Second, the concept of a female androgen deficiency syndrome has remained controversial because of a lack of agreement on an operational definition. Historically, three general approaches have been used to define clinical disorders. For some analytes, such as serum sodium and potassium, we have used a statistical definition in which individuals with serum analyte concentrations below the lower limit of the 95% confidence interval for a healthy population are categorized as having low levels of that analyte. The paucity of rigorously established ranges for testosterone levels in women has limited the use of such a statistical approach. Alternatively, we can use thresholds beyond which the risk of clinical disorders (e.g., bone fracture or cardiovascular disease) is significantly increased. However, for androgen deficiency syndrome in women, we do not know whether there exists a threshold testosterone level below which there is a higher prevalence of related signs and symptoms. A combined approach based on the presence of specific signs and symptoms in combination with laboratory tests has been
applied for the diagnosis of clinical disorders, such as rheumatoid arthritis and systemic lupus erythematosus, wherein composite scores of signs, symptoms, and laboratory tests make the diagnosis of these disorders likely. Many experts in the androgen field favor this approach.

The Princeton Consensus Conference of many thoughtful experts (9, 10), using such a combined approach, proposed three essential criteria for the diagnosis of the female androgen deficiency syndrome. First, the clinical symptoms of androgen deficiency must be present, including diminished sense of well-being or dysphoric mood; persistent, unexplained fatigue; and sexual function changes such as decreased libido, decreased sexual receptivity, and decreased pleasure. Because these symptoms are not specific to androgen deficiency, the panel cautioned that the diagnosis should not be made solely on the basis of symptoms. Many presumed signs and symptoms of androgen deficiency are similar to those of estrogen deficiency and could be affected by estrogens. Therefore, the panel emphasized that the diagnostic criteria of androgen deficiency should be made only in estrogenized women. Third, the free testosterone levels should be at or below the lowest quartile for healthy young women. Recognizing the current difficulties in measuring total and free testosterone levels in women in the setting of clinical practice, the panel shied away from the difficult task of establishing precise quantitative criteria, reflecting a pragmatic rather than a statistical orientation (9, 10).

Robert Koch (1843–1910) proposed four criteria for establishing the causative role of microorganisms in the pathogenesis of human disease. For Koch’s postulates to be fulfilled for female androgen deficiency syndrome, certain minimum expectations must be met. First, low testosterone concentrations must be demonstrable in all cases of female androgen deficiency syndrome. It must be possible to precisely and accurately measure testosterone concentrations in patients and define the syndrome based on established numerical thresholds. Lowering testosterone levels should reproduce the syndrome. Finally, raising testosterone concentrations to the “normal” range in women with low testosterone levels must reverse the signs and symptoms associated with the low testosterone levels. The available data on androgen deficiency syndrome in women do not fulfill Koch’s postulates.

In one of the most comprehensive studies of perimenopausal women, reported in this issue of the JCEM by Santoro et al. (1), testosterone levels were only weakly associated or not associated at all with sexual desire after adjustment for other baseline characteristics such as age, ethnicity, waist circumference, smoking, physical function impairment, or mood. Although epidemiological surveys have observed that testosterone levels are lower in older women than young women (11), they have also reported either no correlation or weak correlations between circulating testosterone levels and measures of sexual function. These data are consistent with the notion that sexual dysfunction in women is a heterogeneous, multifactorial syndrome and that the precise role of androgen deficiency in its pathogenesis remains unclear.

Some have argued that published data and clinical experience demonstrating beneficial effects of androgen supple-

mentation on several domains of sexual function in women after surgical menopause provide evidence for the important role of androgens in regulating sexual function in women and justify testosterone replacement in older women with sexual dysfunction (12–14). However, many published studies describing testosterone supplementation in women with sexual dysfunction, with some notable exceptions (14, 15), used supraphysiological doses of testosterone; these data have been extrapolated to advocate testosterone replacement of all older women with sexual dysfunction. It has been assumed that testosterone dose-response relationships are different in women than in men and that clinically significant effects on psychosocial function, body composition, muscle performance, cognitive function, and other health-related outcomes can be achieved at testosterone doses and concentrations that are substantially lower than those required to produce similar effects in men; however, these assumptions have not been tested rigorously. Furthermore, the premise that the organ systems that are the targets of virilizing side effects, such as the skin, hair, vocal cords, and clitoris, differ in their testosterone sensitivity from androgen-dependent functions that are the site of beneficial effects such as sexual, cognitive, and physical function remains unsubstantiated.

Thus, the female androgen deficiency syndrome remains a plausible hypothesis in search of supporting data. Testosterone supplementation to improve some aspects of sexual function in carefully selected women with sexual dysfunction is being investigated and may be justifiable should the data from long-term studies demonstrate acceptable risk-benefit profile. However, the use of testosterone for the treatment of sexual dysfunction in women with hypoactive sexual desire should be viewed in a pharmacological context rather than hormone replacement therapy. Although some data emerging from well-designed randomized, controlled trials support the plausibility of this hypothesis (14–15), the long-term risks and benefits of pharmacological testosterone supplementation in women remain unknown. Therefore, at present, it is premature to make a general recommendation about testosterone replacement in all older women with low testosterone levels to improve their sexual function and well-being.

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