LETTER TO THE EDITOR

RE: Is There a Correlation Between Androgens and Sexual Desire in Women?

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We were very interested to read the results of the study by Wåhlin-Jacobsen et al. [1] titled "Is there a correlation between androgens and sexual desire in women?" The researchers used mass spectrometry methods to investigate age-adjusted serum levels of dehydroepiandrosterone sulfate (DHEA-S), androstenedione, and testosterone, as well as androsterone glucuronide (ADT-G)—a measure of total androgen activity. The results were consistent with our published study of 121 women with and 124 women without a diagnosis of Hypoactive Sexual Desire Disorder (using the definition of the Diagnostic and Statistical Manual, 4th edition, text-revised), where no group differences in androgen metabolites were found [2].

We were somewhat perplexed by the apparent change in Wåhlin-Jacobsen et al.'s [1] objective in their paper from investigating a possible correlation between serum levels of testosterone and/or androgen metabolites and sexual desire, to finding a measure that does indeed correlate with desire and to apparently suggest its use hereon. The conclusion in the abstract that ADT-G did not correlate more strongly than circulating androgens with sexual desire and therefore is not superior to measuring circulating androgens with mass spectrometry presupposes an established correlation between androgens and sexual desire.

The authors note that "measuring the degradation product of the intracellular testosterone turnover should therefore yield a better estimate of both the intracellular turnover and the total activity of androgens. In contrast to what we expected, however, no statistically significant correlations were established between ADT-G and sexual desire. Therefore, based on these current and previous results, we cannot conclude that ADT-G is a better biomarker of the link between androgens and women's sexual desire than measuring the amount of circulating androgens." (p. 12). An explanation for these findings can, however, be based upon the understanding that the metabolite of androgens chosen as a parameter of total androgenic activity, namely ADT-G, although a logical suggestion, could have to take into account a more complex pattern than originally believed [3]. As mentioned by the authors, it could well be that ADT-G represents only a fraction of all androgen metabolites. In fact, it could be that ADT-sulfate and epi-ADT-G (and likely others) could represent a much larger proportion of androgen metabolites than ADT-G alone. However, since the very low serum levels of testosterone observed in women during their whole life essentially result from some leakage of the intracellular testosterone synthesized locally from DHEA [4], it might be reasonable, at the present time, to measure the precursors of intracellular testosterone, namely serum DHEA, DHEA-S, androstene-3β,17β-diol, and androstenedione. In fact, low serum levels of all these four androgen precursors have been correlated with sexual dysfunction [1,2,5].

The authors did find a correlation between total testosterone, free testosterone, androstenedione, and DHEA-S in the subgroup of women aged 25–44 who were not using any hormonal contraception (n = 168). In our study, 246 women were more stringently recruited to exclude confounds such as any medication potentially altering sexual response and desire, scoring in the clinically significant depressed range on a validated measure of depression, significant relationship conflict, and sexual pain, and this study failed to show a correlation between mass spectrometry-measured serum testosterone and desire but showed a correlation with low serum DHEA-S [2].

We maintain our conclusion [2] that in large samples of women, there is not yet conclusive evidence of a significant correlation between accurately measured total testosterone activity and sexual desire. This is not to say androgen activity may not be important, but at this point, such evidence of a correlation has not been empirically supported. As indicated above, it could well be that serum testosterone is not a reliable marker since it represents only leakage of intracellular testosterone made by the intracellular mechanisms of intracrinology [4].

The conclusion of Wåhlin-Jacobsen et al. [1] that as measurement of ADT-G showed no significant correlation with women's sexual desire, such measurement "did not seem to be an improvement over measuring circulating androgens with MS" (p. 14) suggests that there was a very different a priori objective to the study than what was published. A recent editorial reminds us of the significant dangers inherent to modification of a priori hypotheses and the threat to statistical analyses as well as interpretation of the findings [6]. That the identification/measurement of the most appropriate metabolites of androgens has not yet been determined in no way negates the importance of intracellular testosterone production.

We offer this analogy: the hypothetical investigation of a correlation between intake of vitamin C supplements and susceptibility to influenza. Imagine researchers counting vitamin C supplements taken by patients and finding the numbers to correlate negatively with number of influenza infections. However, when measuring their serum vitamin C levels, no correlation is found between vitamin C levels and cases of influenza. If the researchers then said "from here-on just count vitamin C supplements as this correlates better with influenza susceptibility," perhaps the lack of a scientific demonstration would be more obvious.

In summary, with the strong caveat of relatively lax exclusion criteria, the findings by Wåhlin-Jacobsen et al. have added to the literature on women's sexual desire and androgens, which are based on the currently available most optimal assays for serum androgens and precursor hormones (liquid chromatography-mass spectrometry), and for total (intracellular plus serum) androgens (ADT-G). As in our study [2], precursors of intracellular testosterone correlated with sexual desire in women aged 25–65 years, none of whom were taking systemic sex hormones. In contrast to our study, in the subgroup of 168 women aged 25–45 years, desire also correlated with measures of serum testosterone. It will be important to repeat these measures on this targeted subgroup, but with stricter exclusion criteria as well as the entry criterion of a diagnosis of sexual interest/arousal disorder assessed by detailed interview as currently available questionnaires do not reflect current conceptualization of women's sexual response or current

definitions of what constitutes a disorder [7]. Until such research is done, we remain without evidence-based guidelines for testosterone supplementation in women.

Rosemary Basson, MD, FRCP(UK),*
Allan Young, MD, PhD, FRCPsyche, FRCP(C),†
Lori A. Brotto, PhD,‡ Miriam Driscoll, MD, FRCP(C),*
Shauna Correia, MD, FRCP(C)*, and
Fernand Labrie, MD, PhD§
**Psychiatry, University of British Columbia, Vancouver, BC, Canada; †Psychological Medicine, King's College, London, UK; ‡Obstetrics and Gynecology, University of British Columbia, Vancouver, BC, Canada; §Laval University Hospital, Research Center in Molecular Endocrinology, Oncology, and Human Genomics, Laval University, Laval, QC, Canada*

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