The Impact of Simultaneous Measurement of Testosterone and Androstenedione in Women with Suspected Androgen Excess

Liquid chromatography tandem mass spectrometry (LC-MS/MS) is becoming more widely available in clinical laboratories, allowing the development of methods that measure multiple analytes simultaneously. Moving away from traditional analysis of single analytes may have unexpected consequences, however, as we report here.

An assessment of biochemical androgen status in women is commonly requested when a patient presents with clinical features of hyperandrogenism, such as hirsutism or acne, and also in the investigation of infertility. Conditions that characteristically show androgen excess include polycystic ovarian syndrome (PCOS), congenital adrenal hyperplasia (CAH), and androgen-secreting tumors (1).

Our previous protocol for the assessment of androgen status in females was to measure testosterone before 2nd- and 3rd-line tests measuring sex hormone binding globulin (SHBG) to calculate the free androgen index (FAI) (2) and androstenedione, respectively. Since June 2005, an LC-MS/MS assay for the simultaneous measurement of testosterone and androstenedione in samples from women has been in routine use. To evaluate its impact, we collated data on 1436 women from samples received in the laboratory for assessments of their androgen status between June 2005 and October 2006. Local ethics committee approval was received for this study. The upper limits of our reference intervals were 1.6 nmol/L for testosterone, 4.7 nmol/L for androstenedione, and 6.5 for FAI \(\text{FAI} = (\text{testosterone} / \text{SHBG}) \times 100\) (2).

Of the 1436 participating women, 876 showed no increases of testosterone, androstenedione, or FAI. The samples from the remaining 560 women had at least 1 increased androgen (Fig. 1).

Simultaneous assays provide more information and have faster turnaround times. The provision of steroid values, at no extra expense, allows the clinician to bring more confidence to the acceptance or rejection of diagnoses associated with androgen excess. Here, testosterone, FAI, or both were increased in the samples of 396 women (27.5% of the total). When tested with the old protocol, before LC-MS/MS, these patients would then have undergone measurement of androstenedione concentration. Therefore, these patients received faster service with the simultaneous assay because the androstenedione concentration had already been measured.

An unexpected finding was the identification of a group of 164 patients (11.4% of the total) who had an increased androstenedione concent-

References


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Fig. 1. Venn diagram to show the distribution of results of the 560 samples with 1 or more increased androgen measurements.
tation without increased testosterone or FAI. In these patients, the mean androstenedione concentration was 5.8 nmol/L, with a range of 4.8 nmol/L to 15.3 nmol/L. This group of patients would not have been identified using the old protocol and thus no diagnostic questions would have been raised. The finding of this group of patients raises several questions—most pertinently, is this status a variant of normal, or is it of clinical significance?

Androstenedione is often considered a proandrogen because it requires conversion to testosterone to exert its androgenic effects (3). This characteristic, together with the fact that androstenedione concentrations increase in the 2nd half of the menstrual cycle (4), may suggest that an isolated increase in androstenedione concentration without increased testosterone or increased FAI should be considered biochemical hyperandrogenism.

The specific constituents of increased biochemical androgen action remain to be elucidated. The use of sensitive, functional, androgen-dependent parameters measured under physiological conditions may enable identification and ranking of the most important predictors for hyperandrogenism. Until these in vivo data are available, the role of androgens other than testosterone in the diagnosis of biochemical hyperandrogenism is unknown.

It is also important to consider whether an isolated increased androstenedione value may have a particular clinical significance. A possibility is that some of the patients may have nonclassical CAH. Nonclassical, or late-onset, CAH may share many of the features of PCOS such as acne, hirsutism, and menstrual irregularity, and additional work could include the measurement of 17-hydroxyprogesterone in such patients to further investigate this hypothesis.

References

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