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Androstenedione, Testosterone, and DHT: Reading the Androgen Pathway, Not a Single Point

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ABSTRACT

Rationale. Androgen status is often reduced to a single testosterone value. But testosterone sits in the middle of a metabolic sequence: a weak precursor, androstenedione (A4), lies upstream, and the most potent androgen, dihydrotestosterone (DHT), lies downstream. The same testosterone concentration can arise from — and give rise to — very different states.

Key distinctions. A4 is a weak precursor androgen of adrenal and gonadal origin; testosterone is the principal circulating androgen; DHT is the most potent androgen, a high-affinity, non-aromatizable androgen-receptor ligand generated in target tissues by 5α-reductase. Because each conversion is enzymatic — 17β-HSD (A4↔T), 5α-reductase (T→DHT), and aromatase (T→estradiol, A4→estrone) — the ratios between the three analytes encode enzyme activity and androgen source.

Clinical implications. Measuring all three and reading their ratios localizes androgen excess (adrenal vs. ovarian/gonadal), exposes 5α-reductase and aromatase activity, and makes the predictable metabolic patterns imposed by 5α-reductase inhibitors and aromatase inhibitors legible.

Conclusion. A single androgen is a point; the pathway is the picture. Panel measurement with the ratios yields information no single analyte provides — provided the assay (LC–MS/MS) is accurate across the relevant ranges.

Keywords: androstenedione · testosterone · dihydrotestosterone · 5α-reductase · aromatase · 17β-HSD · T:A4 and DHT:T ratios · hyperandrogenism · LC–MS/MS

1 Background

Androgen assessment in routine practice is commonly a single testosterone measurement. Yet testosterone is a midpoint in a metabolic sequence: a weak precursor (androstenedione) feeds it, a more potent product (dihydrotestosterone) derives from it, and a parallel route converts both to estrogens. Reading only the midpoint discards where the androgen came from and what it becomes. This review makes the case for measuring the three principal androgens together — androstenedione, testosterone, and DHT — and interpreting the ratios that encode the pathway and its enzymes.

2 One pathway, three androgens

Androstenedione (A4), a weak androgen produced by adrenal and gonadal tissue, is converted to testosterone by 17β-hydroxysteroid dehydrogenase (17β-HSD); testosterone is reduced to dihydrotestosterone (DHT) by 5α-reductase (types 1 and 2) in target tissues; and both A4 and

testosterone can exit the androgen pathway to estrogens (estrone and estradiol) via aromatase. DHT is the most potent androgen — the highest-affinity androgen-receptor ligand, and non-aromatizable — and much of its action is intracrine, generated within skin, hair follicle, and prostate.[3,10] The corollary is that the three analytes report different things: A4 reports precursor supply, testosterone reports circulating androgen, and DHT reports potent, tissue-level androgen activation (Figure 2).

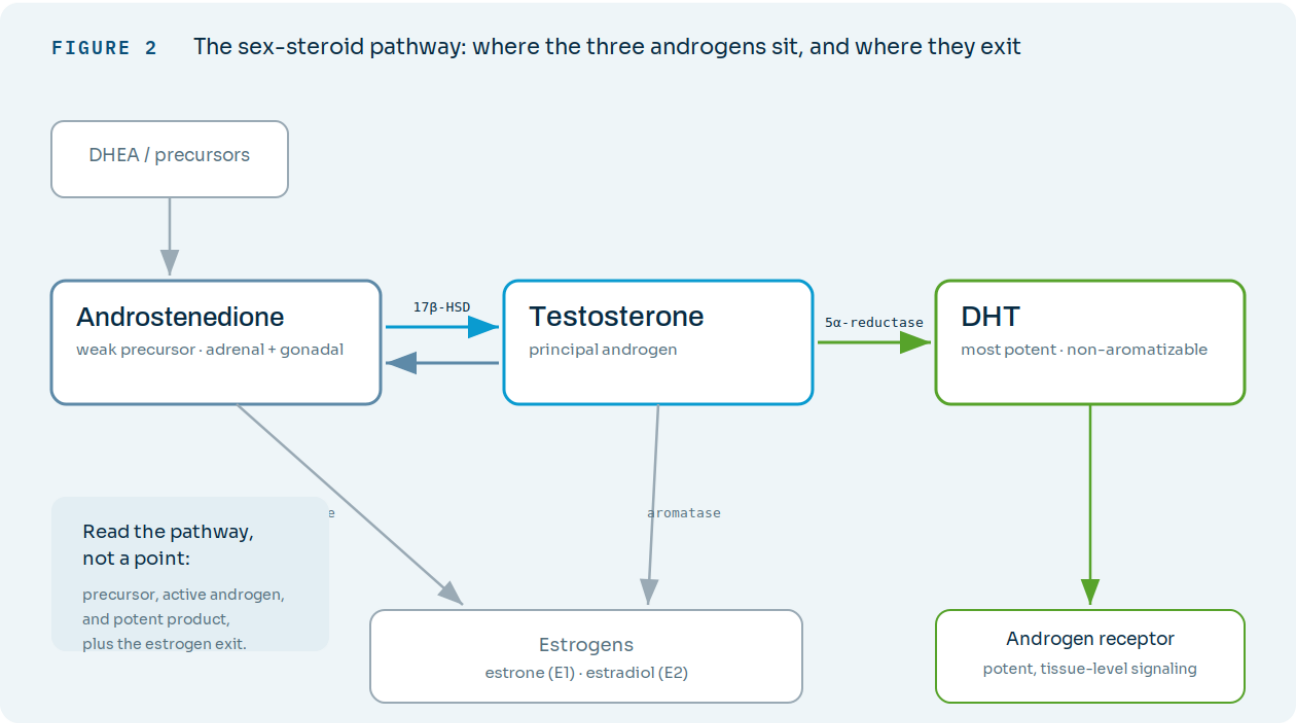

Figure 2. The sex-steroid pathway. Androstenedione is converted to testosterone (17β-HSD) and on to DHT (5α-reductase); both androgens can exit to estrogens via aromatase; DHT is the potent, non-aromatizable androgen-receptor ligand. The three androgens mark precursor, principal hormone, and potent product.

3 The ratios encode enzyme activity and source

Because each step is catalyzed by a distinct enzyme, the ratios between the three analytes are themselves informative. The testosterone-to-androstenedione relationship (T:A4) reflects 17β-HSD conversion of precursor to active androgen; the DHT-to-testosterone relationship (DHT:T) reflects 5α-reductase activity; and a disproportionately high androstenedione points upstream, toward an adrenal or ovarian source or an enzymatic block. In polycystic ovary syndrome, simultaneous LC–MS/MS profiling shows elevated testosterone and androstenedione together with an altered product-to-precursor ratio, localizing the androgen excess to the ovary rather than the adrenal.[2] A single analyte cannot separate these possibilities; the pathway can (Figure 1).

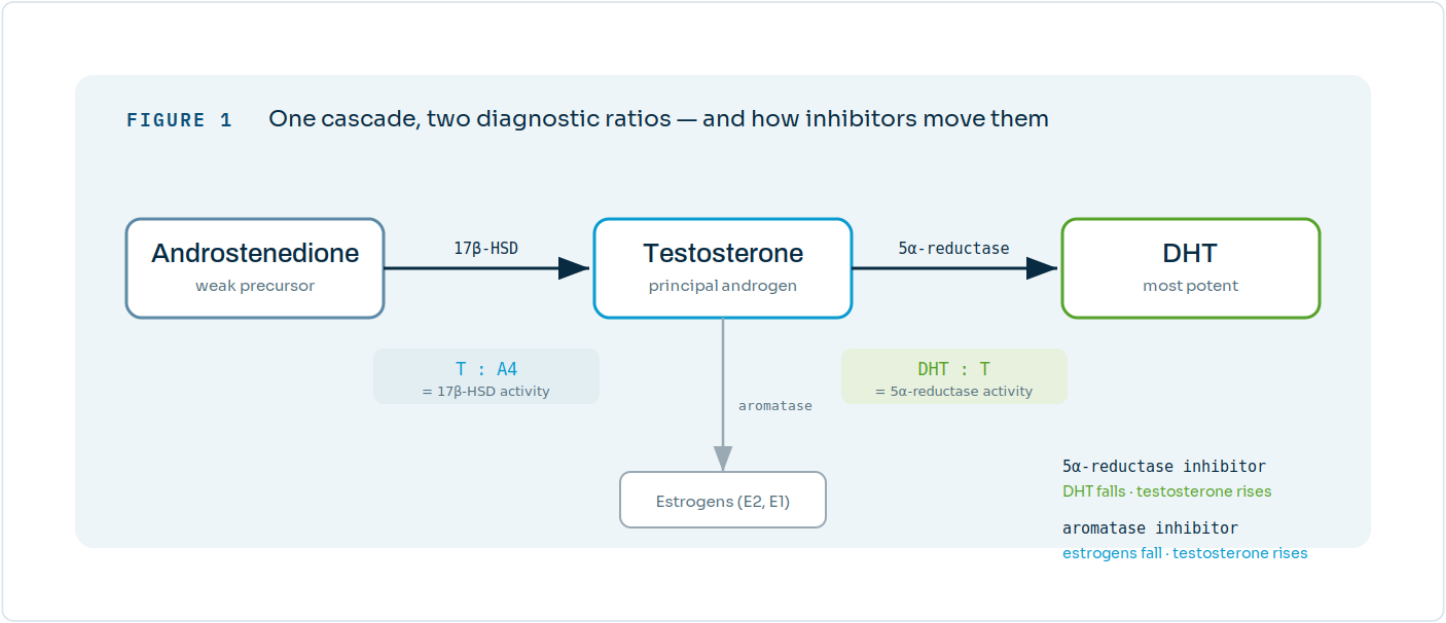

Figure 1. The cascade and its diagnostic ratios. T:A4 indexes 17β-HSD activity and DHT:T indexes 5α-reductase activity; a disproportionate precursor points to source. 5α-reductase inhibitors lower DHT and raise testosterone; aromatase inhibitors lower estrogens and raise testosterone.

4 Metabolic patterns imposed by enzyme inhibitors

Two common therapies rewrite the pathway in predictable, measurable ways. 5α-reductase inhibitors (finasteride, dutasteride) block the conversion of testosterone to DHT: serum and scalp DHT fall — dutasteride lowering DHT more completely than finasteride, dose-dependently — while testosterone rises, inverting the DHT:T ratio.[4] Finasteride reduces circulating DHT by roughly 70%, and prostatic DHT still further.[5] Aromatase inhibitors block the conversion of testosterone to estradiol (and androstenedione to estrone): estrogens fall and androgens accumulate, so testosterone rises as its estrogen exit is closed.[78] In each case, it is measurement of the pathway — not of a single analyte — that makes the shift legible and interpretable.

5 Applications favoring measurement of all three

5.1 Hyperandrogenism and PCOS

Total and free testosterone are the first-line laboratory tests for biochemical hyperandrogenism, with androstenedione (and DHEA-S) adding source information when testosterone is not elevated; the 2023 International PCOS Guideline analysis supports this tiered approach and recommends LC–MS/MS for accuracy.[1] Adding androstenedione and reading the product-to-precursor ratio helps distinguish ovarian from adrenal excess.[2]

5.2 Congenital adrenal hyperplasia

In 21-hydroxylase deficiency, androstenedione — together with 17-hydroxyprogesterone — is a core marker of androgen control, monitored alongside testosterone; LC–MS/MS panels quantify these analytes together for treatment monitoring.[6]

5.3 Androgen-dependent skin and hair conditions

DHT and 5α-reductase drive androgenetic alopecia, hirsutism, and acne.[3] Measuring DHT and the DHT:T ratio characterizes peripheral androgen activation and the response to 5α-reductase inhibition, where DHT falls as testosterone rises.[4]

5.4 Therapy and disease monitoring

The panel tracks the effects of 5α-reductase and aromatase inhibitors, and in prostate cancer it exposes what a single value hides: under androgen deprivation, DHT can persist through intracrine and backdoor synthesis, and androstenedione becomes associated with testosterone in castration-resistant disease — patterns visible only when precursors and products are measured together.[9][10]

6 Analytical considerations

Androgens span a wide dynamic range and are frequently low — in women, in children, and under pharmacologic suppression — where direct immunoassays are unreliable, particularly for androstenedione and DHT; radioimmunoassay overestimates androstenedione relative to mass spectrometry.[2] The 2023 International PCOS Guideline analysis explicitly recommends liquid chromatography–tandem mass spectrometry (LC–MS/MS) for androgen measurement given its accuracy, and validated LC–MS/MS panels quantify androstenedione, testosterone, and DHT — with their precursors — from a single specimen.[1] Laboratories offering accurate, simultaneous measurement therefore report the pathway, not just a point.

Table 1. The three androgens at a glance.

Property	Androstenedione (A4)	Testosterone (T) & DHT
Role	Weak precursor androgen	T: principal androgen · DHT: most potent (highest AR affinity)
Principal source	Adrenal + gonadal	T: testis / ovary + peripheral · DHT: 5α-reduction in target tissue
Key enzyme step	17β-HSD → T; aromatase → estrone	5α-reductase T→DHT; aromatase T→estradiol
Reports	Precursor supply and source	Circulating androgen (T) and potent tissue activation (DHT)
With aromatase inhibitor	Rises (estrogen exit blocked)	Testosterone rises; estrogens fall
With 5α-reductase inhibitor	—	DHT falls sharply; testosterone rises
Preferred assay	LC–MS/MS (immunoassay unreliable)	LC–MS/MS

7 Conclusions and recommendations

Androgen status should not be read from a single point. Measure androstenedione, testosterone, and DHT together and interpret the ratios: T:A4 for precursor conversion, DHT:T for 5α-reductase activity, and a disproportionate precursor for source. Read this way, the panel localizes androgen excess, exposes

enzyme activity, and makes the effects of 5α-reductase and aromatase inhibitors legible — with an assay accurate across the ranges where these questions are actually decided.

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