Unconjugated DHEA and DHEA-Sulfate Are Not Interchangeable: The Clinical Case for Measuring the Active Adrenal Androgen

Clinicore · Clinical Science Team

Department of Endocrine Diagnostics, Clinicore · Laboratory Director: A. Schmidt, MD

CLIA ID 19D2139173 · correspondence — info@clinicorelabs.com · test codes: DHEA (unconjugated) · DHEA-S

ABSTRACT

Rationale. Across clinical practice, "DHEA status" is represented almost universally by dehydroepiandrosterone sulfate (DHEA-S), an analyte selected for its analytical convenience. DHEA-S, however, is a biologically inert sulfoconjugate, whereas unconjugated dehydroepiandrosterone (DHEA) is the receptor-active, intracrine, and neuroactive species.

Key distinctions. The two pools differ by roughly two to three orders of magnitude in concentration and diverge sharply in half-life and temporal behavior: DHEA-S is static, while DHEA is low, short-lived, and secreted in ACTH-driven pulses with diurnal structure. Because sulfotransferase (SULT2A1) and steroid sulfatase (STS) independently govern interconversion, circulating DHEA and DHEA-S can dissociate.

Clinical implications. Measurement of unconjugated DHEA enables assessments the sulfate cannot support — the cortisol:DHEA ratio as an index of hypothalamic–pituitary–adrenal (HPA) balance, monitoring of DHEA replacement, and complete adrenal-androgen characterization when paired with DHEA-S.

Conclusion. DHEA-S remains an appropriate screen for cumulative adrenal androgen output but is an incomplete surrogate for the active hormone. Paired measurement yields information neither analyte provides alone.

Keywords: dehydroepiandrosterone · DHEA-sulfate · adrenal androgens · SULT2A1 · steroid sulfatase · cortisol:DHEA ratio · intracrinology · LC–MS/MS

1 Background

DHEA and DHEA-S are the most abundant circulating steroids in humans, and both decline predictably across the adult lifespan — a decline reproducible enough that DHEA-S is treated as an endocrine biomarker of aging.[1] In routine practice, an order for "DHEA" is fulfilled almost invariably by DHEA-S, because the sulfate circulates at high concentration and is stable throughout the day. That convention is analytically pragmatic, but it has quietly conflated measurability with completeness. The sulfate is easy to measure; it is not, on its own, a faithful readout of the active hormone. This review sets out the biochemical, kinetic, and clinical reasons to treat DHEA and DHEA-S as distinct analytes — and to measure the active hormone when the clinical question calls for it.

2 Two pools of one precursor

DHEA is synthesized in the adrenal zona reticularis and is reversibly sulfated to DHEA-S by cytosolic sulfotransferase SULT2A1; the reverse reaction, desulfation, is catalyzed peripherally by steroid sulfatase (STS). DHEA-S is a hydrophilic circulating reservoir that is biologically inert until desulfation regenerates DHEA. Only the unconjugated hormone is taken up and converted intracellularly — the intracrine pathway — into potent androgens and estrogens within target tissues, and only unconjugated DHEA acts as a neurosteroid at neuronal receptor sites.[2] The clinical corollary is direct: the storage pool reports how much substrate exists; the active pool reports what is physiologically available now (Figure 2).

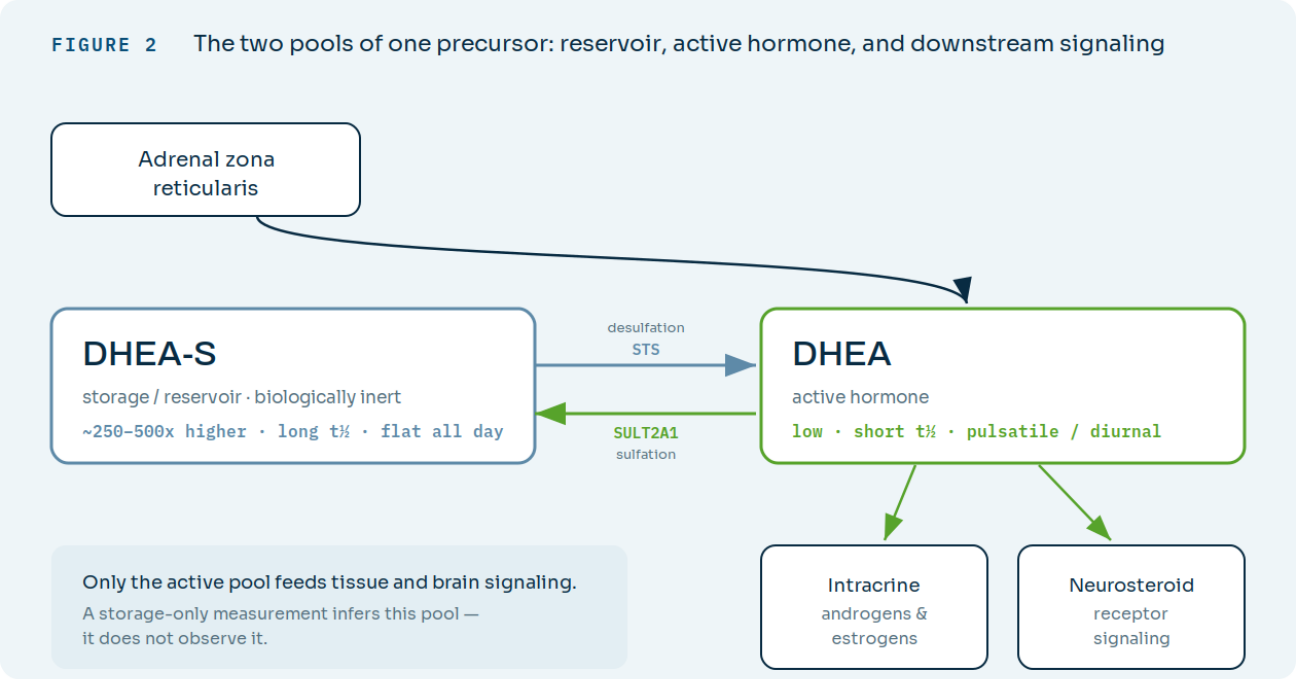

Figure 2. Interconversion architecture. Adrenal DHEA is reversibly sulfated (SULT2A1) and desulfated (STS). Only unconjugated DHEA feeds intracrine androgen/estrogen synthesis and neurosteroid signaling; DHEA-S is an inert reservoir. Independent regulation of the two enzymes allows the pools to move independently.

3 Static reservoir versus dynamic signal

The two analytes carry different temporal information. DHEA-S has high concentration, a long half-life, and minimal diurnal variation — properties that make it a slow-moving, cumulative index. Unconjugated DHEA behaves oppositely: it is present at far lower concentration, has a short half-life, and is secreted in pulsatile, ACTH-driven bursts with clear diurnal and sex-specific structure. In healthy older adults, nocturnal DHEA secretion is pulsatile and sexually dimorphic, and — critically — testosterone administration measurably lowered nocturnal DHEA while morning DHEA-S was unchanged.[3] A static analyte cannot register a dynamic perturbation; the sulfate averages away exactly the signal the active hormone preserves (Figure 1).

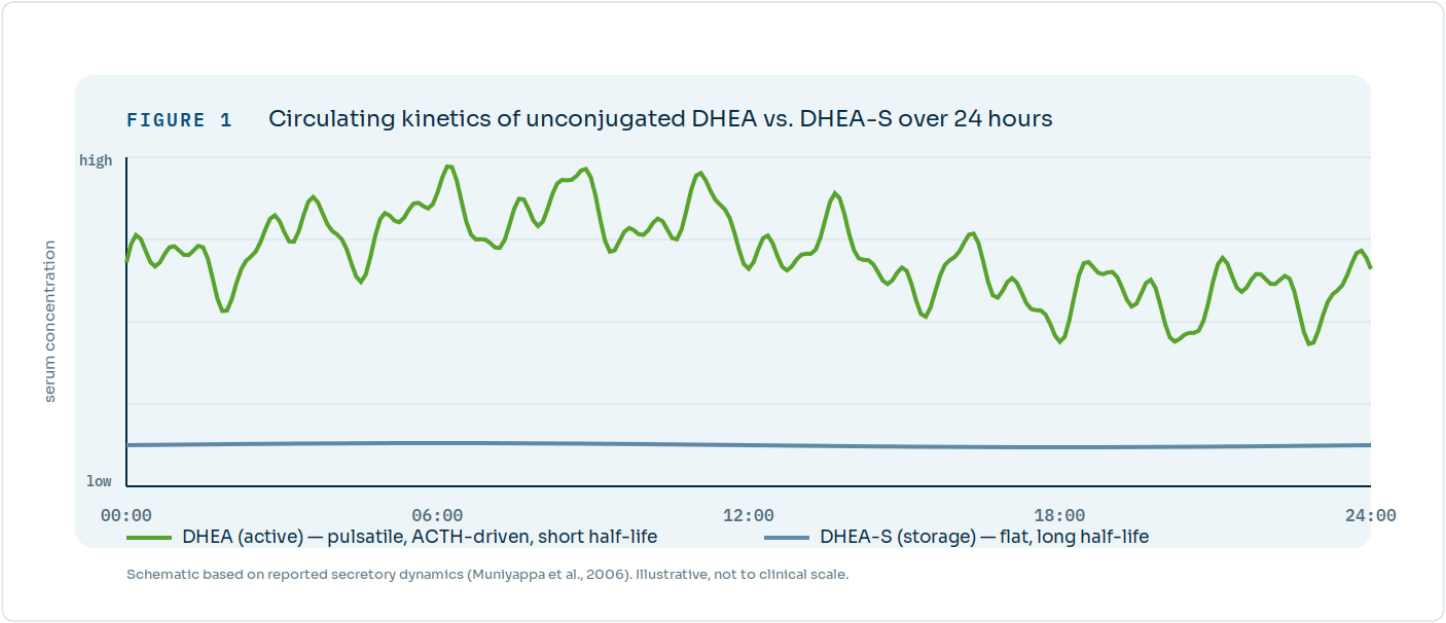

Figure 1. Circulating kinetics over 24 hours. Unconjugated DHEA (green) fluctuates with ACTH-driven pulsatility and a diurnal envelope; DHEA-S (blue) remains essentially flat. Schematic based on reported secretory dynamics;[3] illustrative, not to clinical scale.

4 Dissociation of the two analytes

Because SULT2A1 and STS are regulated independently — by tissue, age, disease state, and pharmacologic exposure — the ratio of DHEA to DHEA-S is not fixed, and the two can move independently. This is demonstrable empirically: in women with childhood sexual-abuse–related post-traumatic stress disorder, 24-hour DHEA-S differed from comparison groups while unconjugated DHEA did not.[4] Where the analytes dissociate, a sulfate-only measurement discards the interconversion signal and can misrepresent active-hormone status. When two markers are capable of diverging, measuring one is a defined blind spot.

5 Applications favoring measurement of unconjugated DHEA

5.1 Cortisol:DHEA ratio and HPA-axis balance

The cortisol:DHEA ratio is used as an index of anabolic–catabolic balance and HPA-axis reactivity; because it requires the active hormone, it cannot be computed from the sulfate. Salivary DHEA and the cortisol:DHEA ratio have been applied to characterize acute stress responsiveness.[5] Panels reporting only DHEA-S cannot furnish this index.

5.2 Monitoring DHEA replacement

Where DHEA is being replaced or supplemented, the unconjugated hormone is the physiologically relevant species to follow. DHEA replacement improves defined outcomes in adrenal insufficiency, with benefit most evident in women,[6] and is an established consideration in the management of adrenal insufficiency.[7] Notably, benefit is condition-specific: controlled data show no clear advantage of DHEA administration in eugonadal older men with a physiological age-related decline,[8] underscoring that the value lies in measuring and interpreting, not in reflexive supplementation.

5.3 Complete adrenal-androgen characterization

DHEA-S remains the appropriate marker of adrenal-derived androgen excess — roughly 20–30% of PCOS patients demonstrate adrenal androgen excess indexed by DHEA-S[9] — and it assists in localizing the source of androgen or cortisol excess in the evaluation of Cushing syndrome and adrenal tumors.[10] Pairing DHEA-S with unconjugated DHEA adds the active-pool and interconversion dimension to that workup rather than replacing it.

5.4 Prognostic context

Low DHEA-S independently predicts all-cause and cardiovascular mortality in men in population cohorts.[11] That prognostic evidence is specific to the sulfate; unconjugated DHEA should be positioned as complementary physiological information, not as a validated substitute prognostic marker. Accurate framing preserves credibility.

6 Analytical considerations

The dominance of DHEA-S in laboratory ordering is, at root, a measurement-driven artifact. Its high concentration and stability make immunoassay straightforward and forgiving of pre-analytical variation. Unconjugated DHEA is analytically more demanding: it circulates at substantially lower concentration, varies through the day, and is susceptible to immunoassay cross-reactivity — so reliable quantification favors a validated liquid chromatography–tandem mass spectrometry (LC–MS/MS) method with appropriate sensitivity and controlled specimen timing. Laboratories able to quantify unconjugated DHEA to this standard therefore report information most panels omit by default.

Table 1. DHEA versus DHEA-S at a glance.

Property	DHEA (unconjugated)	DHEA-S (sulfate)
Biological role	Active precursor; intracrine + neurosteroid	Inert reservoir; requires desulfation
Relative concentration	Low	~250–500× higher
Half-life	Short (hours)	Long (stable across the day)
Diurnal behavior	Pulsatile, ACTH-driven, diurnal	Essentially flat
Information carried	Real-time adrenal output	Cumulative average output
Preferred assay	Validated LC–MS/MS	Immunoassay adequate
Distinct utility	Cortisol:DHEA ratio; therapy monitoring; active-pool status	Screening; aging index; prognostic cohorts

7 Conclusions and recommendations

DHEA-S should not be treated as a proxy for the active hormone. A defensible ordering logic follows from the physiology: screen with DHEA-S for cumulative adrenal androgen output, and add unconjugated DHEA when active-pool status, the cortisol:DHEA ratio, therapy monitoring, or analyte interconversion is clinically relevant. Most importantly, interpret the two together — the relationship between the reservoir and the active hormone is itself informative, and it is invisible when only one is measured.

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