



Reproductive

DHEA-S

Analyte Information



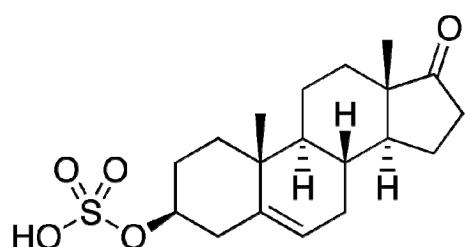


DHEA-S

Introduction

DHEA-S, DHEA sulfate or dehydroepiandrosterone sulfate, it is a metabolite of dehydroepiandrosterone (DHEA) resulting from the addition of a sulfate group. It is the sulfate form of aromatic C₁₉ steroid with 10,13-dimethyl, 3-hydroxy group and 17-ketone. Its chemical name is 3 β -hydroxy-5-androsten-17-one sulfate, its summary formula is C₁₉H₂₈O₅S and its molecular weight (Mr) is 368.5 Da. The structural formula of DHEA-S is shown in (Fig.1).

Fig.1: Structural formula of DHEA-S



Other names used for DHEA-S include: Dehydroisoandrosterone sulfate, (3 β)-3- (sulfoxy), androst-5-en-17-one, 3 β -hydroxy-androst-5-en-17-one hydrogen sulfate, Prasterone sulfate and so on.
As DHEA-S is very closely connected with DHEA, both hormones are mentioned together in the following text.

Biosynthesis

DHEA-S is the major C₁₉ steroid and is a precursor in testosterone and estrogen biosynthesis. DHEA-S originates almost exclusively in the zona reticularis of the adrenal cortex (Fig.2). Some may be produced by the testes, none is produced by the ovaries. The adrenal gland is the sole source of this steroid in women, whereas in men the testes secrete 5% of DHEA-S and 10 – 20% of DHEA. The production of DHEA-S and DHEA is regulated by adrenocorticotropin (ACTH). Corticotropin-releasing hormone (CRH) and, to a lesser extent, arginine vasopressin (AVP) stimulate the release of adrenocorticotropin (ACTH) from the anterior pituitary gland (Fig.3). In turn, ACTH stimulates the adrenal cortex to secrete DHEA and DHEA-S, in addition to cortisol. Negative feedback on CRH, AVP, and ACTH is provided by cortisol. There is no evidence, however, that DHEA-S and DHEA exert feedback on the hypothalamic-pituitary-adrenal (HPA) axis.



Fig.2: Adrenal glands

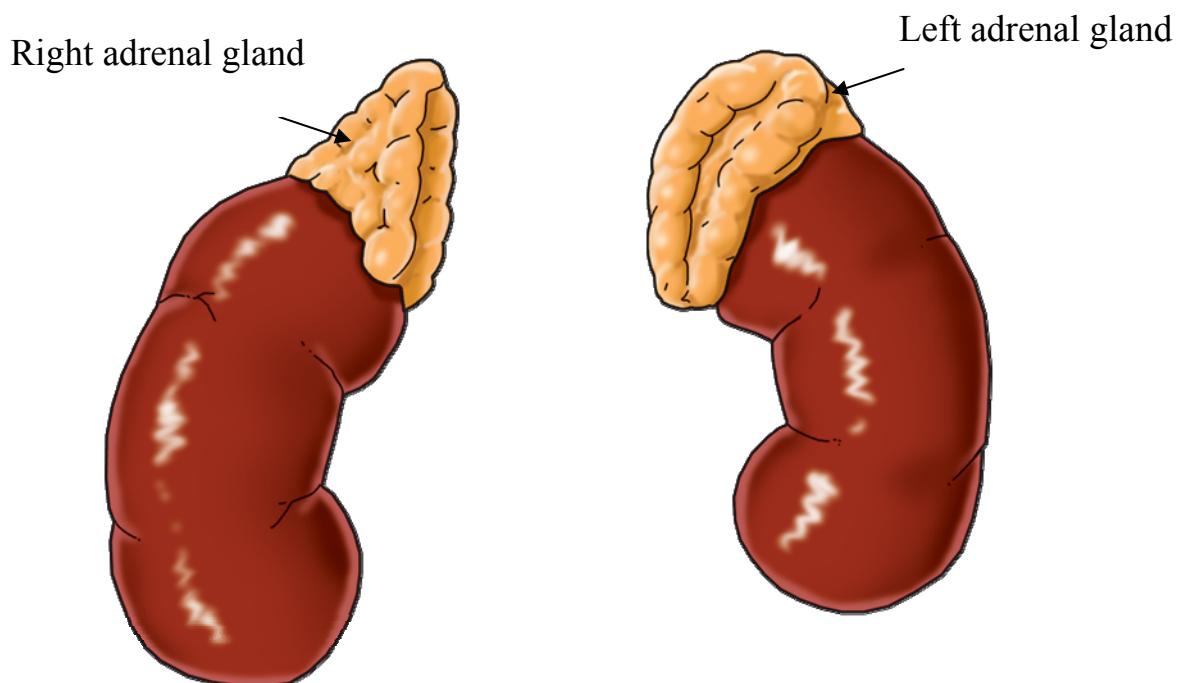
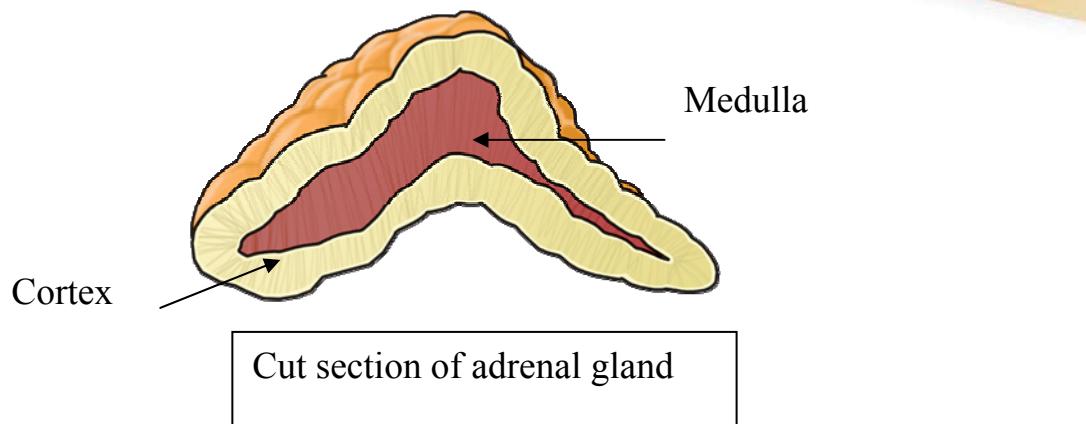
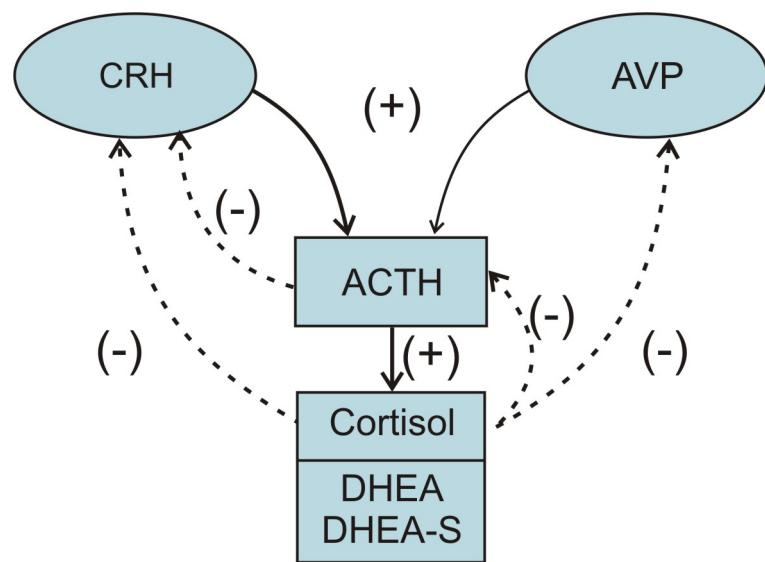




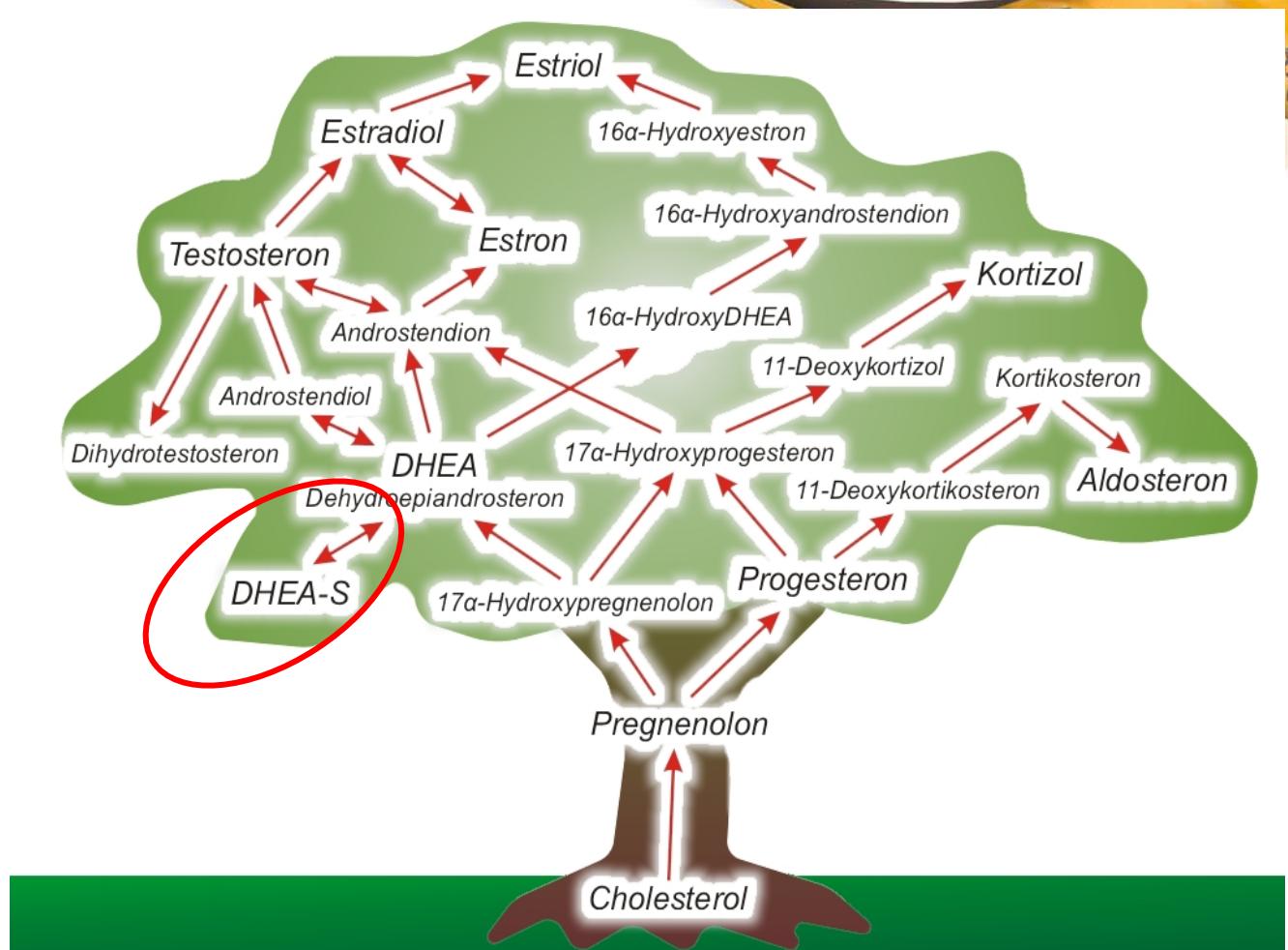
Fig.3: The hypothalamic-pituitary-adrenal (HPA) axis, indicating stimulation (+) and negative feedback (-)



DHEA is produced from cholesterol by two cytochrome P450 enzymes. Cholesterol is converted to pregnenolone by the enzyme P450scc (side chain cleavage). Then another enzyme, P450c17 (17 α -hydroxylase, 17,20 lyase), converts pregnenolone to 17 α -hydroxypregnenolone and then to DHEA¹ (Fig.4). Hydroxysteroid sulfotransferases (SULT2A1) convert DHEA to DHEA-S primarily in the adrenal glands, liver and small intestine.



Fig.4: Steroidogenesis



Metabolism

DHEA-S is the main secreted, circulated and excreted form of DHEA. Most DHEA-S is catabolized and normally only 10% of the steroid is eliminated "as is" in urine. DHEA-S is converted via DHEA into potent androgens and/or estrogens in peripheral tissues^{10,11}.

In gonads and several other tissues (most notably skin), steroid sulfatases can convert DHEA-S back to DHEA.

Both hormones are albumin bound: DHEA weakly, whereas DHEA-S has relatively high affinity to albumin. DHEA-S does not circulate bound to sex hormone binding globulin (SHBG).



The half-life of DHEA-S is 7 – 10 hours and is released at a rate of 10 – 20 mg/day in males and 3.5 – 10 mg/day in females.

Physiological Function

The exact mechanism of action and physiological role of DHEA-S is not well defined. DHEA-S is the major C₁₉ steroid secreted by the adrenal cortex, and is a precursor in testosterone and estrogen biosynthesis. DHEA-S may be viewed as a reservoir of DHEA and DHEA can be understood as the prohormone for the sex steroids. DHEA-S and DHEA serve as the precursors to approximately 50% of androgens in adult men, 75% of active estrogens in premenopausal women, and 100% of active estrogens in postmenopausal women.

However androgenic DHEA-S activity is relatively weak. Nevertheless, the influence of DHEA-S may be increased in cases of relatively high serum concentrations (see example in the paragraph "Levels").

Apart from the fact that DHEA-S functions as a precursor of biologically active androgens and estrogens, the beneficial effects associated with these steroids may be characterized as anticancerotic, antisclerotic, antidiabetic, antiobese and immunostimulatory and immunoprotective. Epidemiological data indicates an inverse relationship between serum DHEA-S and DHEA levels and the frequency of cancer, cardiovascular diseases, Alzheimer's disease, other age-related disorders, immune dysfunction and the progression of HIV infection.

Levels

DHEA-S is the most abundant C₁₉ steroid in humans with serum concentrations 250 – 500 times higher than those of DHEA, 100 – 500 times higher than those of testosterone, and 1,000 – 10,000 times higher than those of estradiol. The typical feature of DHEA-S is a decline of its blood levels with age, as the reticularis layer of the adrenal gland diminishes in size.

As mentioned in the paragraph "Biosynthesis", DHEA-S and DHEA are interconvertible by sulfatases and sulfotransferase in peripheral and adrenal tissues. Once in circulation, around 64% (in women) or 74% (in men) of the DHEA-S produced is metabolized back to DHEA, but only 13% of DHEA is further metabolized back to DHEA-S.

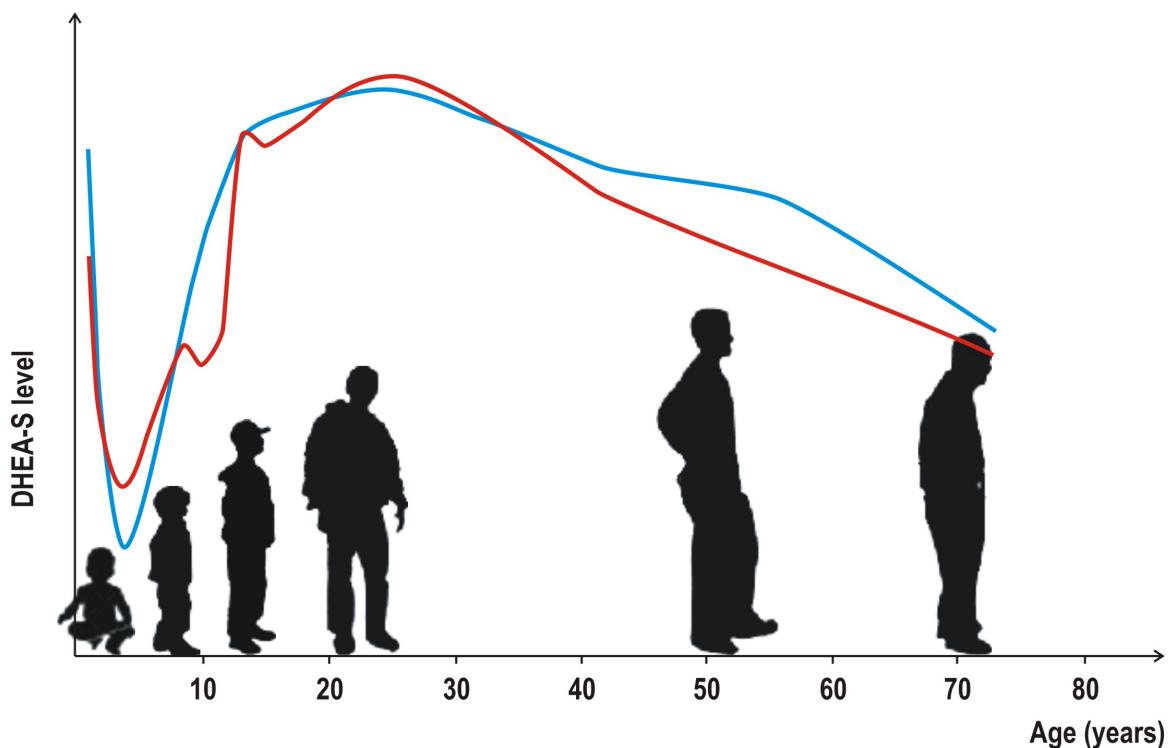
Serum DHEA-S levels are relatively high in the fetus and neonates, are low during childhood, and increase during puberty^{3,4}. The fetal adrenal glands secretes DHEA-S in large quantities. This serves as a precursor in placental production of the dominant pregnancy estrogen – estriol. In the weeks after birth, DHEA-S levels fall by 80% or more and remain low until the onset of adrenarche at age 7 – 8 (in girls) or age 8 - 9 (in boys). At the onset of adrenarche, the adrenal glands gradually resume DHEA-S production, which accelerates through puberty. In young adults, the adrenal cortex secretes approximately 25 mg of



DHEA-S; in contrast, DHEA production is on the level of 4 mg per day. Maximal values of circulating DHEA-S are reached between the ages of 20 and 30.

Thereafter serum DHEA-S levels decrease markedly^{4,6,5} at a rate of 2% per year. By the eighth or ninth decade of life, serum levels are at 10 – 20% of those during peak production years. This age-associated decrease in DHEA-S secretion has been named adrenopause, despite the fact that only DHEA-S production declines, whereas glucocorticoids and mineralocorticoids continue to be secreted without considerable variance.

Fig.5: Changes of DHEA-S levels during the life cycle



Whereas DHEA levels naturally reach their peak in the early morning hours, DHEA-S levels do not exhibit significant diurnal variation. DHEA-S levels show little day-to-day variation, and they are not responsive to acute corticotropin administration⁴. This may be due to the slower metabolic clearance rate (MRC) of DHEA-S compared to that of DHEA⁶. DHEA-S has an MRC of 5 – 20 L/day, while the MRC of DHEA is much higher at 2,000 L/day

DHEA-S levels do not vary significantly during the menstrual cycle².

From a practical point of view, measurement of DHEA-S is more convenient than DHEA, as the levels are more stable.

Circulating concentrations of DHEA-S can be changed by hormone supplements and various drugs.



Typical DHEA-S¹³ levels of children and adult males and females are given in table 1.
For each assay, the relevant reference values are shown in the appropriate Instructions for Use (IFU).

Table 1: Typical DHEA-S levels

| Specimen (serum) | Reference interval (ng/mL) |
|------------------------------|--------------------------------------|
| Newborn (1 - 5 days) | |
| male: | 1,080 – 4,060 |
| female: | 100 – 2,480 |
| 1 month – 5 years | |
| male: | 10 – 410 |
| female: | 50 – 550 |
| 6 – 9 years | |
| male: | 25 – 1,450 |
| female: | 25 – 1,400 |
| Puberty Tanner stage: | |
| Stage I | |
| male: | 50 – 2,650 |
| female: | 50 – 1,250 |
| Stage II | |
| male: | 150 – 3,800 |
| female: | 150 – 1,500 |
| Stage III | |
| male: | 600 – 5,050 |
| female: | 200 – 5,350 |
| Stage IV | |
| male: | 650 – 5,600 |
| female: | 350 – 4,850 |
| Stage V | |
| male: | 1,650 – 5,000 |



female: 750 – 5,300

Adults male

19 – 30 years: 1,250 – 6,190
31 – 50 years: 590 – 4,520

51 – 60 years: 200 – 4,130
61 – 83 years: 100 – 2,850

Adults female

19 – 30 years: 290 – 7,810
31 – 50 years: 120 – 3,790
Postmenopausal: 300 – 2,600

Equation for the conversion of units: 1 ng/mL × 2.7 = nmol/L

Diagnostic utility – prospects and possibilities

Measurement of serum DHEA-S provides a useful marker of androgen biosynthesis. Altered DHEA-S levels can be found in a broad spectrum of disorders, e.g.:

Elevated DHEA-S levels

- Congenital adrenal hyperplasia due to deficiency of 3 β -dehydrogenase, 21-hydroxylase, or 11 β -hydroxylase^{2,6}
- PCOS in women (Polycystic Ovary Syndrome)¹²
- hirsutism (some cases)^{2,8}
- acne in females
- adrenal cortex tumors (values higher in adrenal carcinomas than in adrenal adenomas)⁷
- ectopic ACTH-producing tumor
- Cushing's syndrome
- precocious puberty
- schizophrenia¹⁴
- obesity⁹





Decreased DHEA-S levels

- adrenal insufficiency
- hypopituitarism (low production of pituitary hormones regulating the production and secretion of adrenal hormones)
- delayed puberty
- hyperlipidemia

Diagnostic utility – Practical applications

Elevated DHEA-S/DHEA levels indicate increased adrenal androgen production.

DHEA-S is primarily produced in the adrenal glands and as such is a useful marker of their functioning. The usage of DHEA-S as an indicator is very similar to that of DHEA. Due to a lack of diurnal variation, relatively high levels and no dependence on sex-hormone binding globuline levels, DHEA-S measurement is a very useful diagnostic tool.

Diagnosing and differential diagnosis of hyperandrogenism

An initial screen in adults might include measurement of DHEA-S/DHEA and free testosterone levels. Depending on the results, this may be supplemented with measurements of SHBG and 17 α -hydroxyprogesterone. In women, elevated DHEA-S/DHEA levels may be found in cases of hirsutism, PCOS, acne, and male-pattern baldness. Men are usually asymptomatic, but through peripheral conversion of androgens can occasionally experience mild estrogen excess.

In the diagnosis of congenital adrenal hyperplasia (CAH)

DHEA-S is measured together with cortisol, 17 α -hydroxyprogesterone and androstenedione.

Monitoring of CAH treatment

DHEA-S levels are measured in conjunction with testosterone, 17-OHP, androstenedione and DHEA. In small children, congenital adrenal hyperplasia (CAH-autosomal recessive diseases) due to 3 β -dehydrogenase deficiency is associated with excessive DHEA-S/DHEA production. Lesser elevations may be observed in 21-hydroxylase deficiency (the most common form of CAH) and 11 β -hydroxylase deficiency.



Diagnosis and differential diagnosis of premature adrenarche

DHEA-S is measured in conjunction with FSH, LH, testosterone, free testosterone, 17-OHP, estradiol, DHEA, androstenedione and SHBG. Increased levels of DHEA-S/DHEA during adrenarche may indicate increased risks. In girls, early adrenarche may increase the risk of later polycystic ovary syndrome, and some boys may develop early penile enlargement.

Diagnosis and differential diagnosis of PCOS

Concentrations of DHEA-S/DHEA are often measured along with other hormones such as FSH, LH, prolactin, estrogen, and testosterone to help rule out other causes of infertility, amenorrhea, and hirsutism.

Diagnosis of androgen-secreting adrenal tumor

Elevated DHEA/DHEA-S levels indicate increased adrenal androgen production. Mild elevations in adults are usually idiopathic, but levels five or more times higher than normal may suggest the presence of an androgen-secreting adrenal tumor. DHEA-S/DHEA levels are elevated in more than 90% of patients with such tumors. Carcinomas typically lack the ability to produce downstream androgens, such as testosterone; by contrast, androgen-secreting adrenal adenomas may also produce excess testosterone and secrete lesser amounts of DHEA-S/DHEA.

Others

Low DHEA/DHEA-S levels may be found in cases of deficiency of steroidogenic acute regulatory protein (StAR – a transport protein that regulates cholesterol transfer within the mitochondria) or of 17 α -hydroxylase.

DHEA/DHEA-S assay is important not only as an indicator of active androgen precursors and adrenal function, but also in cases of endocrine auto-immune diseases including both types of diabetes mellitus.



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