

**Over-the-counter delta5 anabolic steroids 5-androsten-3,17-dione; 5-androsten-3beta, 17beta-diol; dehydroepiandrosterone; and 19-nor-5-androsten-3,17-dione: excretion studies in men.**

Uralets VP, Gillette PA.

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Studies of urinary steroids were performed in males after oral administration of 5-androsten-3,17-dione; 5-androsten-3beta,17beta-diol; dehydroepiandrosterone; and 19-nor-5-androsten-3,17-dione. 5-Androsten-3,17-dione; 5-androsten-3beta,17beta-diol; and dehydroepiandrosterone amplify most endogenous steroids, but to a lesser extent than their delta4 analogues do. Especially affected are androsterone, etiocholanolone, dehydroandrosterone, dehydroepiandrosterone, and isomeric 5-androstendiols. 5-Androsten-3,17-dione; 5-androsten-3beta,17beta-diol; and dehydroepiandrosterone elevate the urinary testosterone to epitestosterone (T/E) ratio by a factor of 2-3 a few hours after administration. This may cause a positive T/E test (> 6) for individuals with normal T/E ratios higher than 2. Most of the steroids return to their original concentrations in less than 24 h. Etiocholanolone and 5beta-androstan-3alpha,17beta-diol remain elevated for several days. A reduced androsterone to etiocholanolone (A/E) ratio may be an indication of delta5 steroids abuse. 19-Nor-5-androsten-3,17-dione has a similar effect, except that all metabolites in urine are 19-nor exogenous steroids. Identification criteria for 19-nor-5-androsten-3,17-dione may be the same as nandrolone, that is, detection of 19-norandrosterone and 19-noretiocholanolone. Specific abundant metabolites of 19-nor-5-androsten-3,17-dione are 19-nordehydroandrosterone and 19-nordehydroepiandrosterone. In the later stages of excretion, higher concentration of 19-noretiocholanolone relative to 19-norandrosterone specifically indicates administration of 19-nor delta5 steroids.



**13Consequence of boar edible tissue consumption on urinary profiles of nandrolone metabolites. II. Identification and quantification of 19-norsteroids responsible for 19-norandrosterone and 19-noretiocholanolone excretion in human urine.**

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In previous work (Le Bizec et al., Rapid Commun. Mass Spectrom. 2000; 14: 1058), it was demonstrated that a boar meal intake could lead to possible false accusations of abuse of 17beta-nortestosterone in antidoping control. The aim of the present study was to identify and quantify endogenous 19-norsteroids in boar edible tissue at concentrations that can alter the steroid urinary profile in humans, and lead to excretion of 19-norandrosterone (19-NA) and 19-noretiocholanolone (19-NE). The samples were analysed in two laboratories. The methodologies used for extraction and detection (GC/MS(EI) and LC/MS/MS(APCI+)) are compared and discussed. 19-Norandrostenedione (NAED), 17beta- and 17alpha-nortestosterone (bNT, aNT), and 17beta- and 17alpha-testosterone (bT, aT) were quantified. The largest concentrations of NAED and bNT were observed in testicles (83 and 172 microg/kg), liver (17 and 63 microg/kg) and kidney (45 and 38 microg/kg). A correlation between the bNT and NAED content of a typical meal prepared with boar parts and the excreted concentrations of 19-NA and 19-NE in human urine was demonstrated.

Maturitas. 1982 Dec;4(4):325-32.

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## **1 The production and aromatization of dehydroepiandrosterone in post-menopausal women.**

**Longcope C, Bourget C, Flood C.**

Using infusions of [3H]dehydroepiandrosterone (DHEA) and [14C]oestrogens, the metabolic clearance rates (MCRD) and blood production rates (PDB) of DHEA and the rate of aromatization of DHEA to oestrone and oestradiol were measured in 7 normal post-menopausal women. The mean +/- SEM value for MCRD was 1850 +/- 270 l/day and for PDB was 3.2 +/- 0.6 mg/day. The MCRD value is similar to those reported for young women but PDB is less than those reported for younger women. The mean +/- SEM value for the aromatization rate of DHEA to E1 in 6 women was 0.0058 +/- 0.004 and in 1 woman the aromatization rate of DHEA to E2 was 0.0008. About 30% of the aromatization of DHEA to E1 occurred via the blood pool of androstenedione. However, 20-25% of E1 arose via the aromatization of DHEA to E1 in peripheral tissues without the intermediacy of the blood pool of androstenedione, and thus the peripheral aromatization of DHEA can be an important source of E1 in some women.

Steroids. 2000 Feb;65(2):98-102.

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## **2 Influence of oral dehydroepiandrosterone (DHEA) on urinary steroid metabolites in males and females.**

**Callies F, Arlt W, Siekmann L, Hubler D, Bidlingmaier F, Allolio B.**

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Oral dehydroepiandrosterone (DHEA) replacement therapy may have a multitude of potential beneficial effects and exerts its action mainly via peripheral bioconversion to androgens (and estrogens). A daily dose of 50-mg DHEA has been shown by us and others to restore low endogenous serum DHEA concentrations to normal youthful levels followed by an increase in circulating androgens and estrogens. As the hepatic first-pass effect may lead to a non physiological metabolism of DHEA after oral ingestion we studied the influence of two single DHEA doses (50 and 100 mg) on the excretion of steroid metabolites in 14 elderly males [age 58.8 $\pm$ 5.1 years (mean  $\pm$  SEM)] with endogenous DHEAS levels <1500 ng/ml and in 9 healthy females (age 23.3 $\pm$ 4.1 years) with transient suppression of endogenous DHEA secretion induced by dexamethasone (dex) pretreatment (4x0.5 mg/day/4 days). Urinary steroid profiles in the elderly males were compared to the steroid patterns found in 15 healthy young men (age 28.9 $\pm$ 5.1 years). In the females the results were compared to their individual baseline excretion without dex pretreatment. Urinary steroid determinations were carried out by semiautomatic capillary gas-liquid chromatography. In both genders DHEA administration induced significant increases in urinary DHEA (females: baseline vs. 50 mg vs. 100 mg: 361 $\pm$ 131 vs. 510 $\pm$ 264 vs. 1541 $\pm$ 587 microg/day; males: placebo vs. 50 mg vs. 100 mg: 434 $\pm$ 154 vs. 1174 $\pm$ 309 vs. 4751 $\pm$ 1059 microg/day) as well as in the major DHEA metabolites androsterone (A) and etiocholanolone (Et). Fifty mg DHEA led to an excretion of DHEA and its metabolites only slightly above baseline levels found in young females and in young men, respectively, whereas 100 mg induced clearly supraphysiological values. After 50 mg DHEA the ratios of urinary DHEA metabolites (A/DHEA, Et/DHEA) were not significantly different between elderly males vs. young male volunteers and young healthy females versus their individual baseline levels. In conclusion, an oral dose of 30 to 50 mg DHEA restores a physiological urinary steroid profile in subjects with DHEA deficiency without evidence for a relevant hepatic first-pass effect on urinary metabolites.

Steroids. 1998 Feb;63(2):80-7.

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**3Oral administration of dehydroepiandrosterone to healthy men: alteration of the urinary androgen profile and consequences for the detection of abuse in sport by gas chromatography-mass spectrometry.**

**Dehennin L, Ferry M, Lafarge P, Peres G, Lafarge JP.**

Laboratoire National de Depistage du Dopage, Chatenay-Malabry, France.

Dehydroepiandrosterone (DHEA) replacement therapy as compensation for high age-related decline of DHEA and DHEA sulfate production is a matter of intense investigation, since many beneficial effects have been proven, or are suggested and expected. Therefore, DHEA abuse by athletes has been considered by the International Olympic Committee, which banned the substance recently. As DHEA for oral supplementation is easily available, we decided to investigate the effect on the urinary androgen profile of administration along this route of a single substitution dose of 50 mg. Quantitative analysis by gas chromatography-mass spectrometry with selected ion monitoring demonstrated that the drug was readily absorbed with 50 to 75% recovery of dosing after 24 h, and with glucuro- and sulfoconjugates of DHEA, androsterone, and etiocholanolone as the most abundant metabolites. In agreement with reported data found in blood, conversion of exogenous DHEA to the principal biologically active androgen, testosterone, was low but proven to be real by the administration of deuterium-labeled DHEA and the subsequent identification and quantification of deuterium-labeled testosterone. A concentration threshold of 300 micrograms/L of DHEA glucuronide is proposed for the screening of DHEA abuse in sport, but a single replacement dose can only be detected during 8 h. Such a short detection period is the consequence of considerable first-pass hepatic metabolism and also of the high interindividual variability of circulating and urinary DHEA and DHEA sulfate concentrations.

Clin Endocrinol (Oxf). 1994 Apr;40(4):459-64.

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#### **4Assessment of 5 alpha-reductase activity in hirsute women: comparison of serum androstanediol glucuronide with urinary androsterone and aetiocholanolone excretion.**

**Gilad S, Chayen R, Tordjman K, Kisch E, Stern N.**

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**OBJECTIVE:** Recent evidence suggests that androstanediol glucuronide (AG), a metabolite of dihydrotestosterone (DHT) formed in skin, is frequently elevated in hirsute women, presumably reflecting enhanced 5 alpha-reductase activity. An alternative method of demonstrating 5 alpha-reductase activity is the androsterone (A)/aetiocholanolone (E) ratio in urine. A and E are the 5 alpha- and 5 beta-reduced metabolites, respectively, of androstenedione, which is the principal metabolite of dehydroepiandrosterone (D). Although serum AG and the urinary A/E ratio have both been considered valid methods for assessing 5 alpha-reductase activity, the two have not been previously compared in hirsute women. The present study was undertaken to assess 5 alpha-reductase activity in hirsute

patients as determined by these two different methods. PATIENTS AND MEASUREMENTS: We surveyed 47 untreated women (ages 17-33) with various degrees of hirsutism. Serum testosterone, bioavailable testosterone, dehydroepiandrosterone sulphate, and AG were determined. Additionally, A, E and D were measured in 24-hour collections of urine. RESULTS: For the 47 women, 37 had elevated blood levels of AG (17.4 +/- 2.2, mean +/- SEM; normal < 8 nmol/l), but only 18 of these had an increased urinary A/E ratio (> 1.5). All but one of the remainder had elevated urinary and/or serum androgen levels. Overall, no significant correlation between AG and A/E was observed. There was a highly significant correlation between AG in serum and A in urine ( $r = 0.82$ ,  $P < 0.001$ ). AG was also positively related to dehydroepiandrosterone sulphate ( $r = 0.64$ ;  $P < 0.005$ ), bioavailable testosterone ( $r = 0.6$ ;  $P < 0.001$ ), aetiocholanolone ( $r = 0.58$ ;  $P < 0.001$ ) and total testosterone ( $r = 0.52$ ;  $P < 0.01$ ). In contrast, A/E was not significantly related to androgen production. CONCLUSIONS: There is a poor correlation between AG and the A/E ratio in hirsute women. Although AG may be raised by increased 5 alpha-reductase activity, it is probably also affected by the presence of elevated androgens regardless of 5 alpha-reductase activity.

Life Sci. 1993;52(21):1709-16.

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### **5Comparative effects of dehydroepiandrosterone and related steroids on peroxisome proliferation in rat liver.**

**Rao MS, Ide H, Alvares K, Subbarao V, Reddy JK, Hechter O, Yeldandi AV.**

Department of Pathology, Northwestern University Medical School, Chicago, IL 60611.

Dehydroepiandrosterone (DHEA) is known to induce peroxisome proliferation and peroxisomal enoyl-CoA hydratase/3-hydroxyacyl-CoA dehydrogenase (PBE) mRNA in the rat liver. We have compared the effects of 6 intermediate metabolites of DHEA on the induction of peroxisome proliferation and PBE mRNA. Administration of epiandrosterone, etiocholanolone, androstenedione, estrone or estradiol for 2 weeks in the diet at 0.45% concentration to adult male F-344 rats failed to induce significant increases in peroxisome proliferation and PBE mRNA when compared to the parent compound DHEA. Dietary administration of 5-androstene-3 beta,17 beta-diol (ADIOL) for 2 weeks at 0.45% concentration caused an increase in PBE mRNA and peroxisome proliferation but to a lesser extent than DHEA. Following a single intragastric dose of DHEA an increase in PBE mRNA level was observed in the liver at 1 hr and continued to 16 hrs., but not with its metabolites. These results strongly suggest that DHEA or possibly another yet to be identified metabolite might be responsible for peroxisome proliferation.

J Clin Endocrinol Metab. 1983 May;56(5):930-5.

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## **6Metabolism of dehydroisoandrosterone and androstenedione in human pulmonary endothelial cells in culture.**

**Milewich L, Hendricks TS, Johnson AR.**

The capacity of endothelial cells from pulmonary arteries and veins to convert dehydroisoandrosterone (3 beta-hydroxy-5-androsten-17-one) and androstenedione to potent, biologically active steroids was investigated. The metabolites of [3H]dehydroisoandrosterone produced in pulmonary artery endothelial cells were androstenedione and 5-androstene-3 beta, 17 beta-diol. The metabolites isolated from incubation of pulmonary arterial cells with [3H]androstenedione were testosterone, 5 alpha-androstane-3,17-dione, 5 alpha-dihydrotestosterone (17 beta-hydroxy-5 alpha-androstan-3-one), isoandrosterone (3 beta-hydroxy-5 alpha-androstan-17-one), and androsterone. The products of [3H]androstenedione metabolism in human pulmonary venous cells were the same as those formed in arterial cells, and in addition, 5 alpha-androstane-3 alpha,17 beta-diol and 5 alpha-androstane-3 beta, 17 beta-diol were formed. The rates of metabolite formation from [3H]androstenedione in pulmonary arterial and venous endothelial cells were linear with incubation time up to 3 h. These findings suggest that the pulmonary endothelium is an important site for the metabolism of dehydroisoandrosterone and androstenedione in the human lung. Endothelial cells produce the same metabolites as human lung tissue, with the exception of hydroxylated steroids.

J Clin Endocrinol Metab. 2001 Jan;86(1):146-50.

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## **7Urinary nandrolone metabolites of endogenous origin in man: a confirmation by output regulation under human chorionic gonadotropin stimulation.**

**Reznik Y, Dehennin L, Coffin C, Mahoudeau J, Leymarie P.**

Service d'Endocrinologie, Laboratoire de Biochimie B, Centre Hospitalier Universitaire Cote de Nacre 14033 Caen, France.

19-Nortestosterone (nandrolone) is an anabolic steroid compound widely used as a doping agent by athletes. The analysis of its urinary metabolites, 19-norandrosterone (NA) and 19-noretiocholanolone (NE) glucuronides, allows the detection of surreptitious administration of nandrolone in sport. A threshold concentration at 2 microgram/L urinary nandrolone metabolites is advocated by the International Olympic Committee for the detection of doping, but some controversy concerning the validity of this threshold arose from the demonstration of endogenous production of nandrolone in mammals, including humans. The regulation of human nandrolone production and its contribution in vivo to the

process of aromatization remain unknown. In the present study 10 healthy men were successively submitted to insulinic stress and gonadal stimulation by hCG administration. Urinary NA and NE concentrations were quantified by gas chromatography-mass spectrometry. NA was detected in basal urine samples from all subjects, with a mean urinary excretion rate (UER) of 3.17 +/- 0.35 ng/h, whereas NE was detected in 4 of 10 (UER range, 0.8-4.7 ng/h). Insulinic hypoglycemia did not significantly modify mean NA UER despite random intraindividual variations between timed urine collections. After hCG administration, NA UER increased by 250% ( $P < 0.01$ ) and estradiol (E(2)) UER by 260% ( $P < 0.001$ ). The maximum NA concentration obtained after stimulation was 0.43 microgram/L. NA UER, plasma E(2), and E(2)/T ratio peaked on day 1 after hCG administration, whereas plasma T peaked later on day 3. NA UER correlated with plasma E(2) ( $r = 0.61$ ;  $P < 0.001$ ) and E(2)/T ( $r = 0.51$ ;  $P < 0.001$ ), but not with plasma T. In conclusion, insulinic stress did not significantly alter nandrolone metabolism, whereas the effect of hCG was a stimulation of NA excretion in all subjects, which constitutes strong support for the endogenous origin of low basal NA excretion. The comparative kinetics of NA UER, plasma E(2), and E(2)/T ratio suggest a contribution of the aromatase process to nandrolone biosynthesis in man.

Rapid Commun Mass Spectrom. 2000;14(12):1058-65.

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### **8Consequence of boar edible tissue consumption on urinary profiles of nandrolone metabolites. I. Mass spectrometric detection and quantification of 19-norandrosterone and 19-noretiocholanolone in human urine.**

**Le Bizec B, Gaudin I, Monteau F, Andre F, Impens S, De Wasch K, De Brabander H.**

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For the first time in the field of steroid residues in humans, demonstration of 19-norandrosterone (19-NA: 3alpha-hydroxy-5alpha-estran-17-one) and 19-noretiocholanolone (19-NE: 3alpha-hydroxy-5beta-estran-17-one) excretion in urine subsequent to boar consumption is reported. Three male volunteers agreed to consume 310 g of tissues from the edible parts (meat, liver, heart and kidney) of a boar. The three individuals delivered urine samples before and during 24 h after meal intake. After deconjugation of phase II metabolites, purification and specific derivatisation of target metabolites, the urinary extracts were analysed by mass spectrometry. Identification was carried out using measurements obtained by gas chromatography/high resolution mass spectrometry (GC/HRMS) ( $R = 7000$ ) and liquid chromatography/tandem mass spectrometry (LC/MS/MS) (positive electrospray ionisation (ESI+)). Quantification was realised using a quadrupole mass filter. 19-NA and 19-NE concentrations in urine reached 3.1 to

7.5 microg/L nearby 10 hours after boar tissue consumption. Levels returned to endogenous values 24 hours after. These two steroids are usually exploited to confirm the exogenous administration of 19-nortestosterone (19-NT: 17beta-hydroxyestr-4-en-3-one), especially in the antidoping field. We have thus proved that eating tissues of non-castrated male pork (in which 17beta-nandrolone is present) might induce some false accusations of the abuse of nandrolone in antidoping. Copyright 2000 John Wiley & Sons, Ltd.

J Chromatogr B Biomed Sci Appl. 1999 Feb 19;723(1-2):157-72.

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## **9Evidence for the presence of endogenous 19-norandrosterone in human urine.**

**Le Bizec B, Monteau F, Gaudin I, Andre F.**

LDH-LNR, Ecole Nationale Veterinaire, Nantes, France.

In 1997, in the scope of antidoping control in sport, a not inconsiderable number of urine analysed by official laboratories revealed the presence of 19-nortestosterone (19-NT: 17beta-hydroxyestr-4-en-3-one) metabolites: 19-norandrosterone (19-NA: 3alpha-hydroxy-5alpha-estran-17-one) and 19-noretiocholanolone (19-NE: 3alpha-hydroxy-5beta-estran-17-one). These repeated results on a short period of time generated some investigations and especially the verification of the possible production of these metabolites by an unknown endogenous route in adult entire male. Some experiences were led on different persons known to be non-treated with steroids and more precisely with nandrolone. Extractive methods were developed focusing on their selectivity, i.e. searching to eliminate at best matrix interferences from the target analytes. Gas chromatography coupled to mass spectrometry (quadrupole and magnetic instruments) was used to detect, identify and quantify the suspected signals. Two types of derivatization (TMS and TBDMS), a semi-preparative HPLC as well as co-chromatography proved unambiguously the presence, in more than 50% of the analysed urine (n = 40), of 19-NA at concentrations between 0.05 and 0.60 ng/ml. 19-NE was not detected with the developed methods (LOD<0.02 ng/ml). Experiments led on athletes showed that after a prolonged intense effort, the 19-NA concentration can be increased by a factor varying between 2 and 4. Even if some complementary researches have to be done in order to determine the maximal physiological level of 19-NA and 19-NE, these results should considerably change the strategy of antidoping laboratories.

J Chromatogr B Biomed Sci Appl. 1999 Jan 22;721(2):301-7.

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## **10Urinary excretion of 19-norandrosterone of endogenous origin in man: quantitative analysis by gas chromatography-mass spectrometry.**

**Dehennin L, Bonnaire Y, Plou P.**

Laboratoire de la Federation Nationale des Courses Francaises, Chatenay-Malabry, France.

A GC-MS method, using deuterium-labelled 19-noretiocholanolone as internal standard and following an extensive LC purification prior to selected ion monitoring of the bis(trimethylsilyl) ethers at ion masses  $m/z$  405, 419, 420 and 421, allowed the quantitation of subnanogram amounts of 19-norandrosterone present in 10-ml urine samples at  $m/z$  405. Thirty healthy men, free of anabolic androgen supply, delivered 24-h urine collections in 4 timed fractions. Accuracy was proven by the equation, relating added (0.05-1 ng/ml) to measured analyte, which had a slope not significantly different from 1. Precision (RSD) was 4% at a concentration of 0.4 ng/ml, and 14% at 0.04 ng/ml. Analytical recovery was 82%. The limit of quantitation was 0.02 ng/ml. The excretion ranges were 0.03-0.25 microg/24 h or 0.01-0.32 ng/ml in nonfractionated 24-h urine. Taking into account inter-individual variability and log-normal distribution, a threshold of 19-norandrosterone endogenous concentration of 2 ng/ml, calculated as the geometric mean plus 4 SD, was established. This value corresponds to the decision limit advised by sport authorities for declaring positive (anabolic) doping with nandrolone.

J Chromatogr. 1991 Apr 5;564(2):393-403.

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**11 Detection of 19-nortestosterone and its urinary metabolites in miniature pigs by gas chromatography-mass spectrometry.**

**Debruyckere G, Van Peteghem C.**

Laboratory of Food Analysis, Faculty of Pharmaceutical Sciences, State University of Ghent, Belgium.

The metabolism of 19-nortestosterone was investigated in a miniature non-castrated male pig (boar), in a castrated pig (barrow) and in a female pig (sow). Urine samples were taken before and at regular intervals after the injection of 100 mg of Laurabolin (nortestosterone laurate). The sample clean-up consists in preliminary solid-phase extraction, followed by high-performance liquid chromatographic purification and fractionation. Finally, gas chromatography-mass spectrometry is used to identify the 19-nortestosterone metabolites.

J Steroid Biochem Mol Biol. 2001 Oct;78(4):351-7.

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**12 Endogenous origin of norandrosterone in female urine: indirect**

**evidence for the production of 19-norsteroids as by-products in the conversion from androgen to estrogen.**

**Van Eenoo P, Delbeke FT, de Jong FH, De Backer P.**

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Recently the use of high resolution mass spectrometry or tandem mass spectrometry has enabled the detection of low amounts of anabolic steroids. As a consequence, the post-administration detection time of these drugs has been extended. Recent investigations have shown that norandrosterone, previously unequivocally regarded as evidence of nandrolone administration, might be an endogenous steroid present in small amounts in urine of humans. In this study, very low concentrations (<1 ng/ml) of norandrosterone in urine of a female athlete were detected using tandem mass spectrometry. The presence of norandrosterone was strongly correlated with high plasma 17beta-estradiol levels during the menstrual cycle. Analysis of urine samples from pregnant women supports the hypothesis of formation of precursors for urinary 19-norandrosterone during aromatization of androgens to estrogens. The detection of low urinary concentrations of norandrosterone (0.2-0.5 ng/ml) in samples after strenuous exercise could be regarded as an additional evidence for the existence of such a pathway.

Biochemistry. 2005 Aug 16;44(32):10839-45.

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**14Aromatase reaction of 3-deoxyandrogens: steric mode of the C-19 oxygenation and cleavage of the C10-C19 bond by human placental aromatase.**

**Numazawa M, Nagaoka M, Sohtome N.**

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Aromatase is a cytochrome P-450 enzyme complex that catalyzes the conversion of androst-4-ene-3,17-dione (AD) to estrone and formic acid through three sequential oxygenations of the 19-methyl group. To gain insight into the catalytic function of aromatase as well as the mechanism of the hitherto uncertain third oxygenation step, we focused on the aromatase-catalyzed 19-oxygenation of 3-deoxyandrogens: 3-deoxy-AD (1), which is a very powerful competitive inhibitor but poor substrate of aromatase, and its 5-ene isomer 4, which is a good competitive inhibitor and effective substrate of the enzyme. In incubations of their

19S-(3)H-labeled 19-hydroxy derivatives 2 and 5 and the corresponding 19R-(3)H isomers with human placental microsomes in the presence of NADPH under air, the radioactivity was liberated in both water and formic acid. The productions of (3)H(2)O and (3)HCOOH were blocked by the substrate AD or the inhibitor 4-hydroxy-AD, indicating that these productions are due to a catalytic function of aromatase. A comparison of the (3)H(2)O production from S-(3)H substrates 2 and 5 with that from the corresponding R-(3)H isomers revealed that the 19-pro-R hydrogen atom was stereospecifically (pro-R:pro-S = 100:0) removed in the conversion of 5-ene substrate 5 into the 19-oxo product 6, whereas 75:25 stereoselectivity for the loss of the pro-R and pro-S hydrogen atoms was observed in the oxygenation of the other substrate, 2. The present results reveal that human placental aromatase catalyzes three sequential oxygenations at C-19 of 3-deoxyandrogens 1 and 4 to cause the cleavage of the C(10)-C(19) bond through their 19-hydroxy (2 and 5) and 19-oxo (3 and 6) intermediates, respectively, where there is a difference in the stereochemistry between the two androgens in the second 19-hydroxylation. It is implied that the aromatase-catalyzed 19-oxygenation of 5-ene steroid 4 but not the 4-ene isomer 1 would proceed in the same steric mechanism as that involved in the AD aromatization.

Cancer Res. 1982 Aug;42(8 Suppl):3277s-3280s.

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### **15 Biochemical mechanism of aromatization.**

#### **Fishman J.**

The aromatization of androgens to estrogens by placental aromatase involves three hydroxylations which take place in sequence. The first two occur at the C-19-methyl group while the site of the final and rate-determining hydroxylation has been identified as being at 2 beta. The product of this reaction collapses to estrogen by a rapid nonenzymatic mechanism. The absence of a direct relationship between the enzyme(s) responsible for estrogen formation and the end product results in an absence of product feedback inhibition, a consequence with potential physiological implications. The proposed mechanism of estrogen formation is supported by chemical, biochemical, and immunological evidence.

Am J Psychiatry. 2006 Jan;163(1):59-66.

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### **16 Placebo-controlled trial of dehydroepiandrosterone (DHEA) for treatment of nonmajor depression in patients with HIV/AIDS.**

#### **Rabkin JG, McElhiney MC, Rabkin R, McGrath PJ, Ferrando SJ.**

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**OBJECTIVE:** Subsyndromal major depressive disorder is common among HIV-positive adults. This study was designed to assess the efficacy of dehydroepiandrosterone (DHEA) as a potential treatment. **METHOD:** One hundred forty-five patients with subsyndromal depression or dysthymia were randomly assigned to receive either DHEA or placebo; 90% (69 of 77) of the DHEA patients and 94% (64 of 68) of the placebo patients completed the 8-week trial. The primary measure of efficacy was a Clinical Global Impression improvement rating of 1 or 2 (much or very much improved) plus a final Hamilton Depression Rating Scale score  $\leq 8$ . Outcome was assessed by using intent-to-treat analysis, followed by completer analysis. Safety was assessed by queries about side effects at every study visit plus measures of CD4 cell count and HIV RNA viral load at baseline and week 8. DHEA dosing was flexible (100-400 mg/day). **RESULTS:** On the basis of clinicians' ratings, DHEA was superior in the intent-to-treat analysis, where the response rate was 56% (43 of 77) for the DHEA group versus 31% (21 of 68) for the placebo group. In the completer analysis, the response rate was 62% (43 of 69) for the DHEA group, compared to 33% (21 of 64) for the placebo patients. The number needed to treat was 4 on the basis of intent-to-treat data and 3.4 on the basis of completer data. Few adverse events were reported in either treatment group, and no significant changes in CD4 cell count or HIV RNA viral load were observed in either group. **CONCLUSIONS:** Nonmajor but persistent depression is common in patients with HIV/AIDS, and DHEA appears to be a useful treatment that is superior to placebo in reducing depressive symptoms. The low attrition rate in this group of physically ill patients, together with requests for extended open-label treatment, reflect high acceptance of this readily available intervention.

Clin Endocrinol (Oxf). 2001 Sep;55(3):325-30.

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**17 Double-blind placebo-controlled trial of oral dehydroepiandrosterone in patients with advanced HIV disease.**

**Piketty C, Jayle D, Leplege A, Castiel P, Ecosse E, Gonzalez-Canali G, Sabatier B, Boulle N, Debuire B, Le Bouc Y, Baulieu EE, Kazatchkine MD.**

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**OBJECTIVE:** Plasma levels of dehydroepiandrosterone sulphate (DHEA-S) decrease with the progression of HIV disease. Here, we report on the efficacy and safety of the oral administration of DHEA as replacement therapy, in patients with advanced HIV disease, in a trial that was primarily aimed at assessing quality of life. **DESIGN:** The trial was randomized and double-blind. Thirty-two patients were allocated to either DHEA 50 mg per day for 4 months (n = 14) or a matching placebo (n = 18). Clinical data, virological and immunological surrogate markers

of HIV infection, plasma levels of DHEA-S and the Medical Outcomes Study HIV Health Survey (MOS-HIV) quality of life scale were recorded every month. RESULTS: The mean age of the patients was 40 +/- 11 years. The mean CD4 cell count at baseline was 32.5 +/- 32.4 x 10(6)/l. The mean DHEA-S plasma level at baseline was 5.23 +/- 0.76 micromol/l. No side-effects related to DHEA occurred during the study. A statistically significant increase in the levels of DHEA-S was observed in the treated group throughout the study (P < 0.01). A significant improvement in the Mental Health and Health Distress dimension of MOS-HIV was observed in the DHEA treated group; P = 0.001 and 0.004, respectively. No change in CD4 cell counts was seen during follow-up. CONCLUSIONS: The administration of DHEA in patients with advanced HIV infection results in improved mental function scores as assessed by the MOS-HIV quality of life scale.

J Acquir Immune Defic Syndr. 1993 May;6(5):459-65.

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### **18An open-label dose-escalation trial of oral dehydroepiandrosterone tolerance and pharmacokinetics in patients with HIV disease.**

**Dyner TS, Lang W, Geaga J, Golub A, Stites D, Winger E, Galmarini M, Masterson J, Jacobson MA.**

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Dehydroepiandrosterone (DHEA) is a naturally occurring adrenal steroid reported to have immunomodulatory and antiviral activity in cellular and animal models as well as modest in vitro antiretroviral activity against human immunodeficiency virus (HIV). A phase I dose-escalation study was performed to evaluate the safety and pharmacokinetics of DHEA in subjects with symptomatic HIV disease and an absolute CD4 lymphocyte count between 250 and 600 cells/microliters. Thirty-one subjects were evaluated and monitored for safety and tolerance. The oral drug was administered three times daily in doses ranging from 750 mg/day to 2,250 mg/day for 16 weeks. Some immunological and virological parameters were monitored as well. The drug was well tolerated and no dose-limiting side effects were noted. Dose proportionality was evidenced neither by the serum DHEA nor by DHEA-S time-concentration curves for the three dosing groups. However, the study cohort appeared to consist of two subpopulations with markedly different bioavailability for a given DHEA dose. No sustained improvements in CD4 counts nor decreases in serum p24 antigen or beta-2 microglobulin levels were observed. However, serum neopterin levels decreased transiently by 23-40% at week 8 compared with baseline in all dosing groups. DHEA was well tolerated by patients with mild symptomatic HIV disease; evaluation of this agent for efficacy in HIV disease would require randomized, controlled trials.

Psychopharmacology (Berl). 2005 Oct 18;:1-11 [Epub ahead of

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**19 Effects of DHEA administration on episodic memory, cortisol and mood in healthy young men: a double-blind, placebo-controlled study.**

**Alhaj HA, Massey AE, McAllister-Williams RH.**

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**RATIONALE:** Dehydroepiandrosterone (DHEA) has been reported to enhance cognition in rodents, although there are inconsistent findings in humans. **OBJECTIVES:** The aim of this study was to investigate the effects of DHEA administration in healthy young men on episodic memory and its neural correlates utilising an event-related potential (ERP) technique. **METHODS:** Twenty-four healthy young men were treated with a 7-day course of oral DHEA (150 mg b.d.) or placebo in a double blind, random, crossover and balanced order design. Subjective mood and memory were measured using visual analogue scales (VASs). Cortisol concentrations were measured in saliva samples. ERPs were recorded during retrieval in an episodic memory test. Low-resolution brain electromagnetic tomography (LORETA) was used to identify brain regions involved in the cognitive task. **RESULTS:** DHEA administration led to a reduction in evening cortisol concentrations and improved VAS mood and memory. Recollection accuracy in the episodic memory test was significantly improved following DHEA administration. LORETA revealed significant hippocampal activation associated with successful episodic memory retrieval following placebo. DHEA modified ERPs associated with retrieval and led to a trend towards an early differential activation of the anterior cingulate cortex (ACC). **CONCLUSIONS:** DHEA treatment improved memory recollection and mood and decreased trough cortisol levels. The effect of DHEA appears to be via neuronal recruitment of the steroid sensitive ACC that may be involved in pre-hippocampal memory processing. These findings are distinctive, being the first to show such beneficial effects of DHEA on memory in healthy young men.

Arthritis Rheum. 2002 Nov;46(11):2924-7.

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Comment in:

- Curr Rheumatol Rep. 2003 Oct;5(5):348-9.

**20 Dehydroepiandrosterone treatment of women with mild-to-moderate systemic lupus erythematosus: a multicenter randomized,**

**double-blind, placebo-controlled trial.**

**Chang DM, Lan JL, Lin HY, Luo SF.**

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**OBJECTIVE:** To evaluate the efficacy and tolerability of dehydroepiandrosterone (DHEA) at a dosage of 200 mg/day in adult women with active systemic lupus erythematosus (SLE). **METHODS:** In a multicenter randomized, double-blind, placebo-controlled trial, 120 adult women with active SLE received oral DHEA (200 mg/day; n = 61) or placebo (n = 59) for 24 weeks. The primary end point was the mean change from baseline in the Systemic Lupus Activity Measure (SLAM) score at 24 weeks of therapy. Secondary end points included time to first flare, change in SLE Disease Activity Index (SLEDAI) score, and physician's and patient's global assessment scores at week 24. **RESULTS:** The two groups were well balanced for baseline characteristics. Mean reductions in SLAM scores from baseline were similar and were not statistically significantly different between treatment groups (DHEA -2.6 +/- 3.4 versus placebo -2.0 +/- 3.8, mean +/- SD). The number of patients with flares was decreased by 16% in the DHEA group (18.3% of DHEA-treated patients versus 33.9% of placebo-treated patients; P = 0.044, based on time to first flare). The mean change in the patient's global assessment was statistically significant between the two groups (DHEA -5.5 versus placebo 5.4; P = 0.005). The number of patients with serious adverse events, most of which were related to SLE flare, was significantly lower in DHEA-treated patients compared with placebo-treated patients (P = 0.010). Expected hormonal effects, including increased testosterone levels and increased incidence of acne, were observed. No life-threatening reactions or serious safety issues were identified during this study. **CONCLUSION:** The overall results confirm that DHEA treatment was well-tolerated, significantly reduced the number of SLE flares, and improved patient's global assessment of disease activity.

1: Fertil Steril. 2004 Mar;81(3):595-604.

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**Pharmacokinetics of dehydroepiandrosterone and its metabolites after long-term daily oral administration to healthy young men.**

**Acacio BD, Stanczyk FZ, Mullin P, Saadat P, Jafarian N, Sokol RZ.**

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**OBJECTIVE:** To determine the effects of dehydroepiandrosterone (DHEA) supplementation on the pharmacokinetics of DHEA and its metabolites and the reproductive axis of healthy young men. **DESIGN:** A prospective, randomized, double-blind, placebo-controlled pharmacokinetic study. **SETTING:** General

Clinical Research Center and laboratories at the Keck School of Medicine of the University of Southern California, Los Angeles, California. PATIENT(S): Fourteen healthy men, ages 18-42 years. INTERVENTION(S): Daily oral administration of placebo (n = 5), 50 mg DHEA (n = 4), or 200 mg DHEA (n = 5) for 6 months. Blood samples were collected at frequent intervals on day 1 and at months 3 and 6 of treatment. MAIN OUTCOME MEASURE(S): Quantification of DHEA, DHEA sulfate (DHEAS), androstenedione, T, E(2), dihydrotestosterone (DHT), and 5alpha-androstane-3alpha-17beta-diol glucuronide (ADG). Physical examination, semen analysis, serum LH, FSH, prostate-specific antigen, and general chemistries were carried out. RESULT(S): Baseline DHEA, DHEAS, and ADG levels increased significantly from day 1 to months 3 and 6 in the DHEA treatment groups but not in the placebo group. No significant changes were observed in pharmacokinetic values. Clinical parameters were not affected. CONCLUSION(S): DHEA, DHEAS, and ADG increased significantly during 6 months of daily DHEA supplementation. Although the pharmacokinetics of DHEA and its metabolites are not altered, sustained baseline elevation of ADG, a distal DHT metabolite, raises concerns about the potential negative impact of DHEA supplementation on the prostate gland.