Reproductive

Androstanediol glucuronide

Analyte Information

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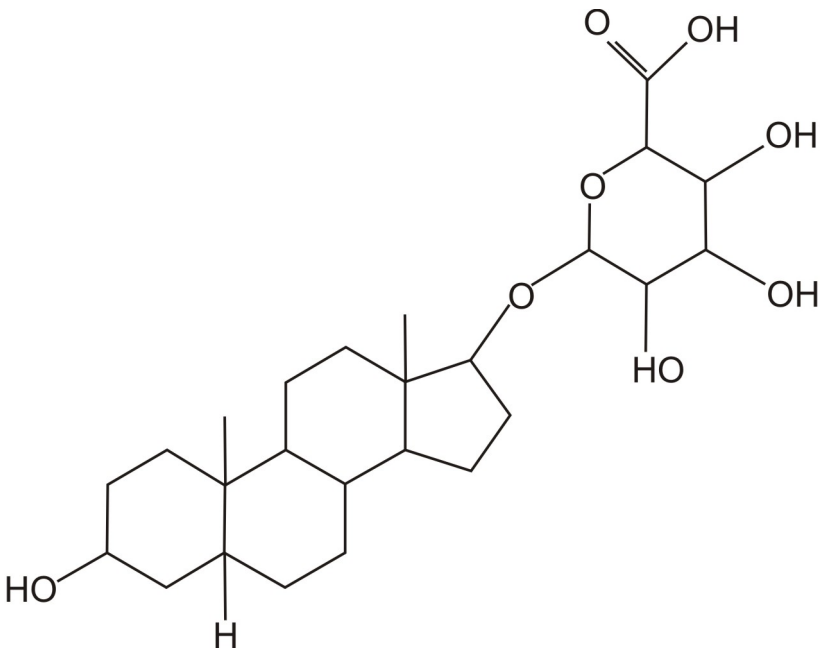
Introduction

3α-androstanediol glucuronide (3α-diol G) is the major metabolite of dihydrotestosterone (DHT)[1], a steroid hormone that belongs to the group of androgens.

Its summary formula is $C_{25}H_{40}O_8$ and its molecular weight (Mr) is 468.58 Da.

The structural formula of androstanediol glucuronide is displayed in Fig.1.

Fig.1: Structural formula of androstanediol glucuronid



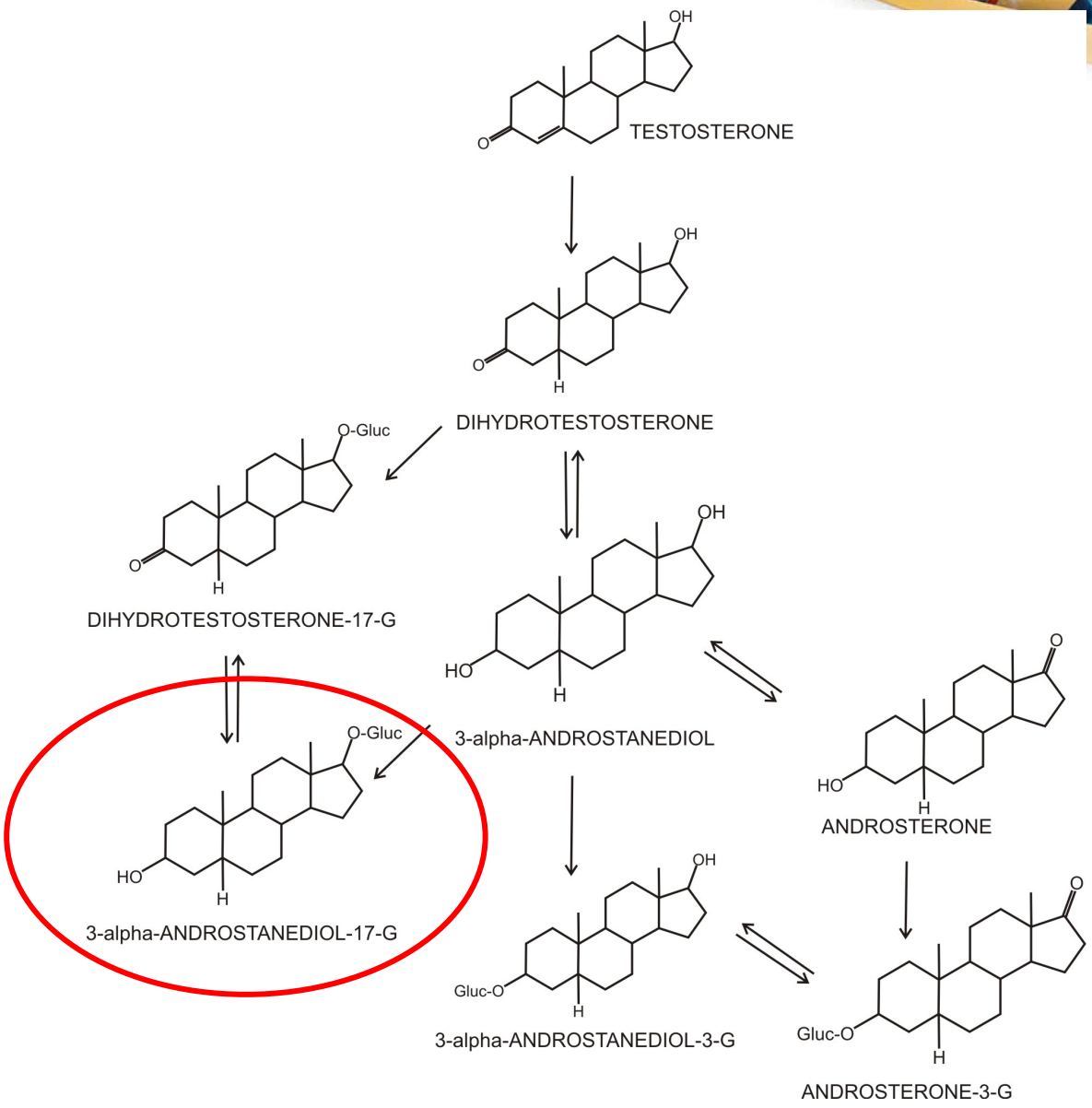
3α-androstanediol glucuronide can be found also under following names: 3α-diol G; adiol G; 5-alpha-androstane-3α, 17β-diol glucuronide; androstane-3alpha, 17beta-diol 3-D-glucuronide; androstane-3alpha, 17beta-diol 3-delta-glucuronide.

Biosynthesis

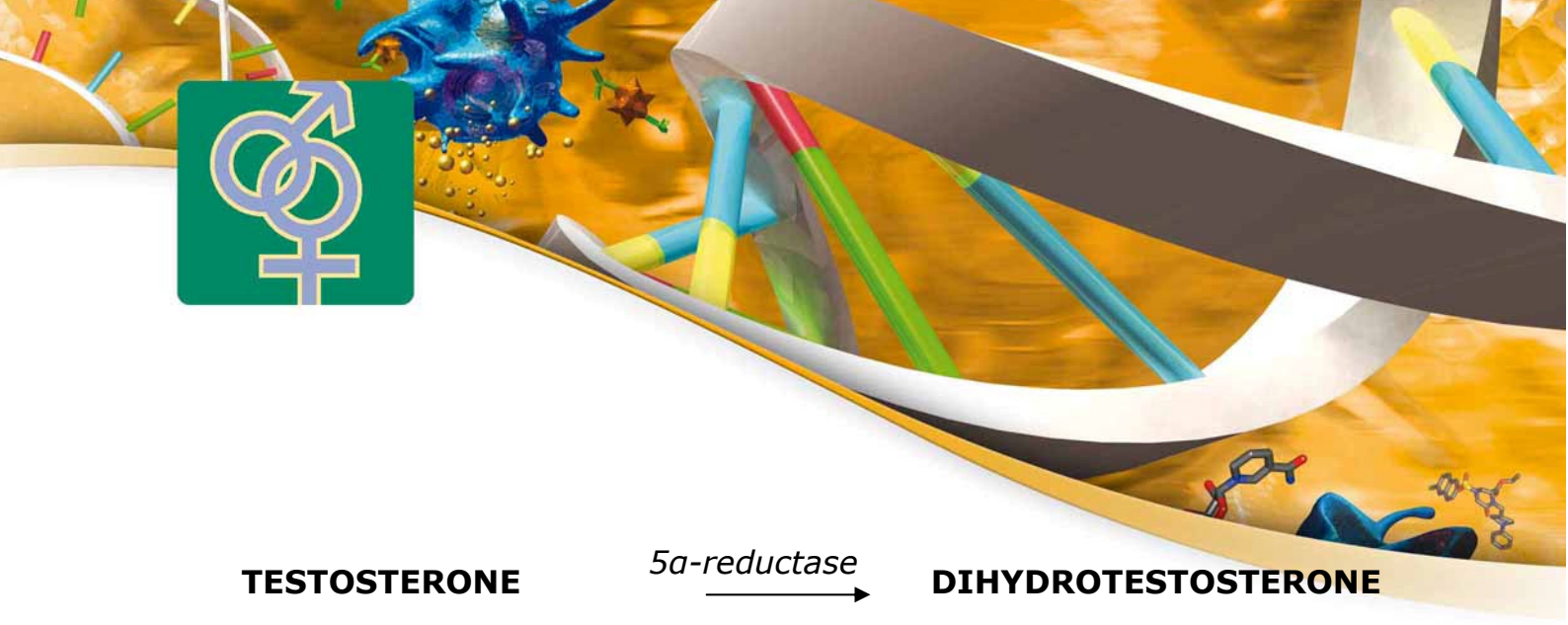
3α-androstanediol glucuronide is by-product of intracellular reduction of DHT (Fig.2). A certain proportion of serum androstanediol may also be derived from dehydroepiandrosterone sulfate (DHEA-S) and androstenedione (ASD). Hence

3α-androstanediol and 3α-androstanediol glucuronide are products of androgens degradation.

Fig.2: Androgens conversion



Androgens such as testosterone or androsterone are not able to produce biological effects in tissues (skin and external genitalia) without first being metabolized[2]. These androgens are first converted by the enzyme 5α-reductase (activated in genital skin[3]) to the more potent dihydrotestosterone (DHT). DHT is further transformed via 3α-androstanediol to 3α-androstanediol glucuronide.



TESTOSTERONE —*5α-reductase*→ **DIHYDROTESTOSTERONE**

DIHYDROTESTOSTERONE —*3α-hydroxysteroid dehydrogenase (3 αHSD)*→ **3α-ANDROSTANEDIOL**

3α-ANDROSTANEDIOL —*UDP glucuronosyl-transferase*→ **3α-ANDROSTANEDIOL GLUCURONIDE**

The sites of androstanediol glucuronidation have not been conclusively defined, supposed sites include the skin and liver[1,4,5]. Glucuronidation is caused by uridine 5'-diphospho-glucuronosyltransferase (UDP glucuronosyltransferase). 3α-androstanediol glucuronide may also be synthesized directly from glucuronidated precursors, including androsterone glucuronide[1].

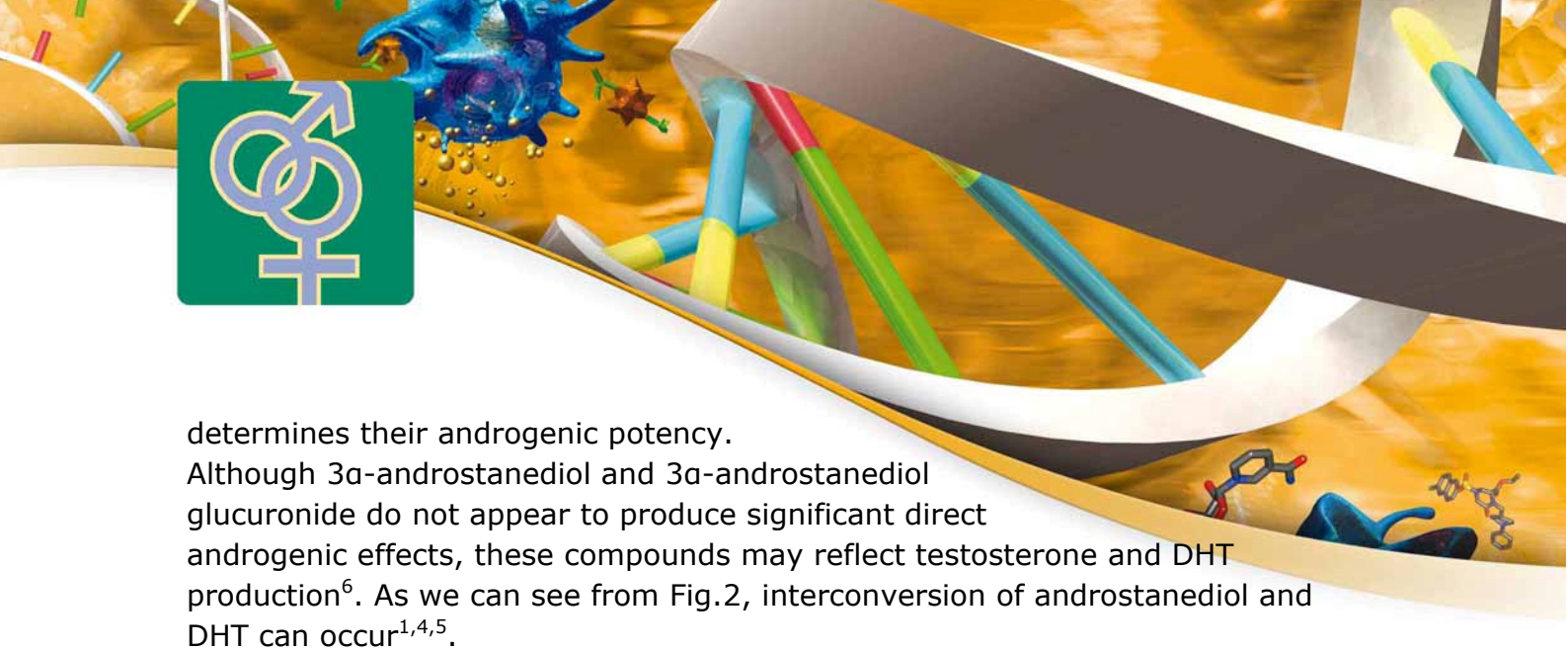
3α-Androstanediol glucuronide actually represents two different compounds since glucuronide can be conjugated at the 3-carbon position (Adiol 3-G) or at the 17-carbon position (Adiol 17-G). It has been shown that Adiol 17-G is the predominant circulating form of 3α-androstanediol glucuronide in healthy men and women and that it is also a major 3α-androstanediol glucuronide isomer derived from DHT.

Metabolism

3α-androstanediol glucuronide terminates the process of testosterone degradation. In general, glucuronidation is used to assist in the excretion of toxic substances, drugs or other substances that cannot be used as an energy source. Glucuronic acid is attached via a glycosidic bond to the substance; the resulting glucuronide, which has higher water solubility than the original substance, is eventually excreted by the kidneys.

Physiological Function

3α-androstanediol glucuronide and 3α-androstanediol are C_{19} steroids.
The presence of a 17-hydroxyl group (retained from testosterone and DHT)



determines their androgenic potency.
Although 3α-androstanediol and 3α-androstanediol glucuronide do not appear to produce significant direct androgenic effects, these compounds may reflect testosterone and DHT production[6]. As we can see from Fig.2, interconversion of androstanediol and DHT can occur[1,4,5].

As mentioned in the paragraph "Metabolism", the main function of 3α-androstanediol glucuronide is to enable inactivation and urinary excretion of DHT metabolites.

Levels

As circulating levels of 3α-androstanediol glucuronide are influenced by the secretion of adrenal and ovarian precursors, it is important to be aware that the androstanediol glucuronide level alone should not be used for diagnostic purposes. Androstanediol glucuronide levels may be elevated due to the increased production of androstenedione and/or testosterone. That said, when these precursor levels are normal, the presence of elevated androstanediol glucuronide may indicate increased peripheral androgen metabolism.

Serum levels of 3α-androstanediol glucuronide decrease after adrenal suppression with glucocorticoids, implying an important adrenal contribution to its formation[8,9]. Similarly, ovarian suppression and stimulation studies have demonstrated that this marker is influenced by ovarian precursors, principally androstenedione and testosterone[10]. It has been shown that long-term GnRH (gonadotropin-releasing hormone) agonist therapy, which suppresses ovarian hormone production, significantly reduces androstanediol glucuronide levels and that this reduction correlates significantly with the improvement of hirsutism[11].

Typical 3α-androstanediol glucuronide [7] levels of children and adult males and females are given in the table 1.

For each assay, the relevant reference values are shown in the appropriate Instructions for Use (IFU).

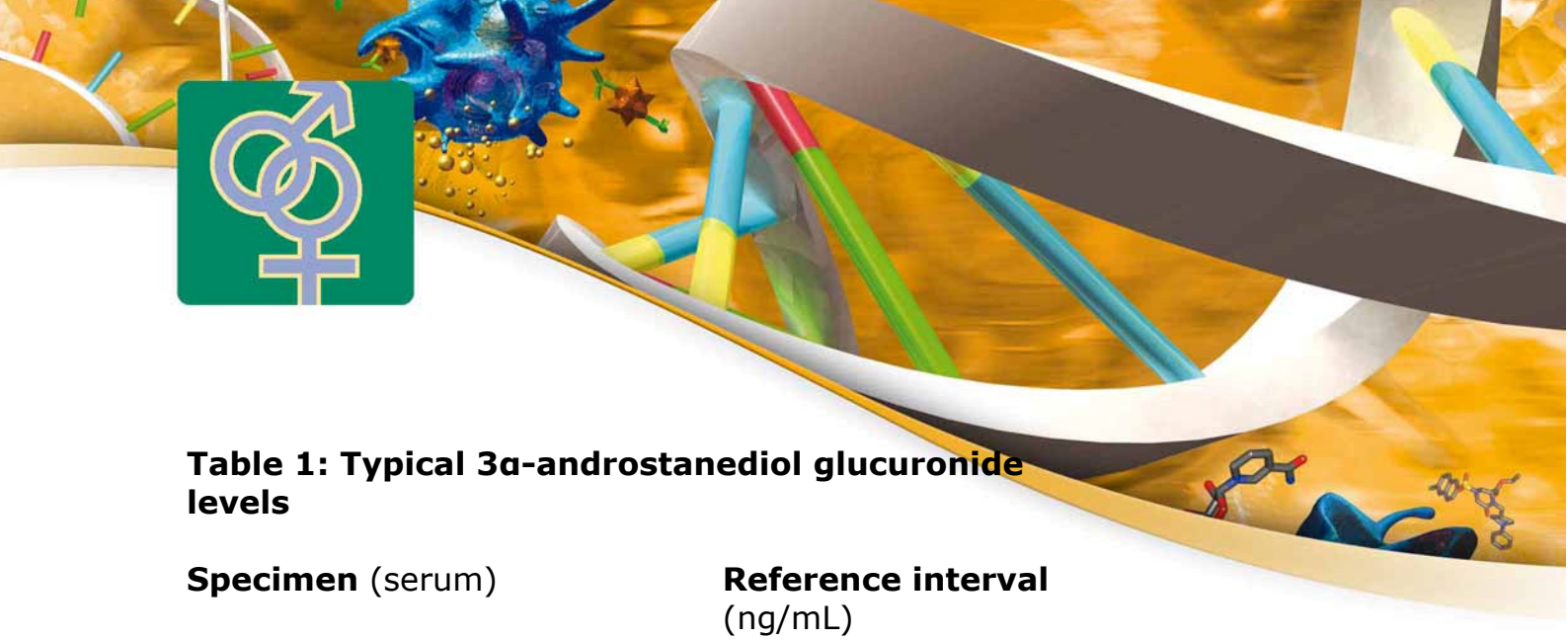


Table 1: Typical 3α-androstanediol glucuronide levels

Specimen (serum)	**Reference interval** (ng/mL)
Children (pre-pubertal):	0.10 – 0.60
Adult men:	2.60 – 15.0
Adult women:	0.60 - 3.00

Equation for the conversion of units: 1 ng/mLx2.13 = nmol/L

Diagnostic utility – prospects and possibilities

Measurement of serum 3α-androstanediol glucuronide provides a useful marker of androgen degradation. Abnormal 3α-androstanediol glucuronide levels can be found in various disorders, e.g.:

Elevated 3α-androstanediol glucuronide levels

- idiopatic hirsutism
- hirsutism associated with polycystic ovary syndrome (PCOS)
- acne in females
- congenital adrenal hyperplasia (CAH)

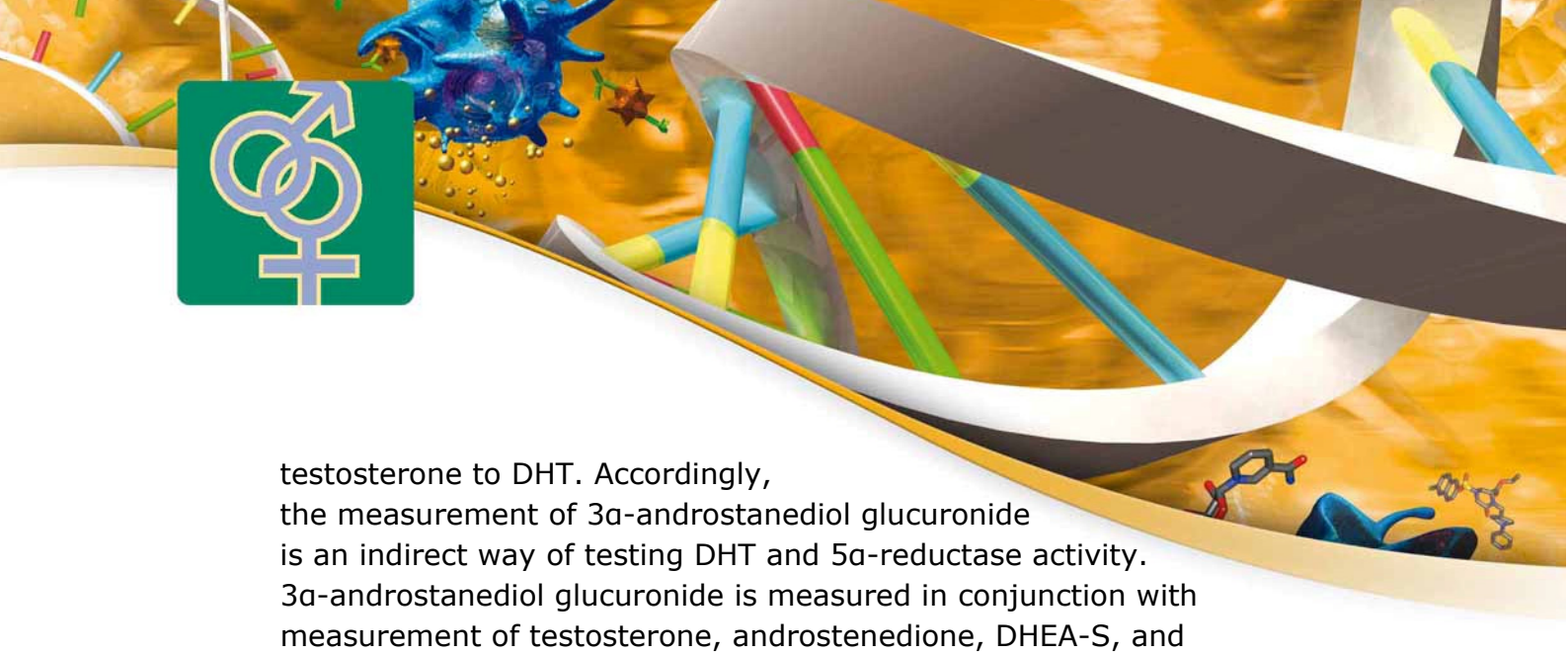
Decreased 3α-androstanediol glucuronide levels

- disorders of androgen action in men
  (e.g., male pseudohermaphroditism)
- dexamethasone administration in hirsute women [8]

Diagnostic utility – Practical application – Clinical information

Management of diseases with excessive androgen production

The measurement of 3α-androstanediol glucuronide is a means of assessing skin androgen activity. The skin's sensitivity to androgens depends on the presence of 5α-reductase enzyme, which converts



testosterone to DHT. Accordingly, the measurement of 3α-androstanediol glucuronide is an indirect way of testing DHT and 5α-reductase activity. 3α-androstanediol glucuronide is measured in conjunction with measurement of testosterone, androstenedione, DHEA-S, and 17 hydroxyprogesterone levels. 3α-androstanediol glucuronide is a better marker than 3α-androstanediol because once formed, no conversion to DHT takes place. 3α-androstanediol can be converted through sulfuryl-transferase to androstanediol sulfatase [12].

Diagnosis, differential diagnosis, therapy monitoring in hirsutism

A direct correlation between serum 3α-androstanediol glucuronide levels and 5α-reductase activity was found in both normal and hirsute women[6]. Serum levels of 3α-androstanediol glucuronide correlate well with the presence and severity of hirsutism[2]. In hirsute patients' serum, 3α-androstanediol glucuronide levels also correlate with a clinical diagnosis of hirsutism based on a Ferriman-Gallwey score[13].

The test is useful in differential diagnosis of hirsutism, in connection with other markers, especially when levels of circulating androgens (testosterone, free testosterone, and DHT) are within normal limits[7].

The measurement of 3α-androstanediol glucuronide in patients being treated for hirsutism is also a useful means to monitor clinical response to therapy[7]. Hirsutism in women has a variety of causes, including the effects of drugs, androgen overproduction by the ovaries or adrenal glands, as well as unknown causes (idiopathic hirsutism). In the case of ovarian androgen overproduction, elevated levels of androstenedione, testosterone, DHT and 3α-androstanediol glucuronide are seen. In adrenal androgen overproduction, DHEA-S levels are increased as well. In some hirsute patients, the capacity of the hair follicle to convert testosterone to DHT is increased. Several studies have shown that in hirsute women, either with polycystic ovary syndrome (PCOS) or idiopathic hirsutism (IH), the activity of 5α-reductase in the genital skin was increased. Measurement of 3α-androstanediol glucuronide is a method by which to indirectly determine the activity of this enzyme.

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