Best Practice & Research Clinical Endocrinology & Metabolism
Vol. 20, No. 2, pp. 177–191, 2006
doi:10.1016/j.beem.2006.03.007
available online at http://www.sciencedirect.com

2

Diagnosis of hyperandrogenism: Biochemical criteria

Frank Z. Stanczyk* PhD

Professor of Research

Departments of Obstetrics and Gynecology and Preventive Medicine, University of Southern California, Keck School of Medicine, Women's and Children's Hospital, Room 1M2, 1240 North Mission Road, Los Angeles, CA 90033, USA

Biochemical derangements in ovarian, adrenal, and peripheral androgen production and metabolism play an important role in underlying causes of hyperandrogenism. Specific diagnostic serum markers such as testosterone (total) and dehydroepiandrosterone sulfate (DHEAS), respectively, may be helpful in the diagnosis of ovarian and adrenal hyperandrogenism, respectively. Validated immunoassays or mass spectrometry assays should be used to quantify testosterone, DHEAS and other principal androgens. Free testosterone measurements, determined by equilibrium dialysis or the calculated method, are advocated for routine evaluation of more subtle forms of hyperandrogenism. The skin, with its pilosebaceous units (PSUs), is an important site of active androgen production. A key regulator in PSUs is 5α-reductase, which transforms testosterone or androstenedione to dihydrotestosterone (DHT). DHT in blood is not effective in indicating the presence of hyperandrogenism. However, distal metabolites of DHT have been shown to be good markers of clinical manifestations of hirsutism, acne and alopecia. Assays for these peripheral markers need improvement for routine clinical testing.

Key words: hyperandrogenism; androgens; testosterone; free testosterone; 5α-reductase; hirsutism; acne; alopecia.

Patients with hyperandrogenism present with a variety of clinical manifestations, among, which hirsutism, acne and alopecia are very common. Derangements of androgen production and metabolism play an important role in the underlying causes of androgenic effects on female skin. To understand these causes, the clinician must be familiar with normal and abnormal androgen production and metabolism, as well as factors that modulate androgen action, in women. An understanding of clinical conditions associated with hyperandrogenism also requires knowledge about the

* Tel.: +1 323 226 3220; Fax: +1 323 226 2850.
E-mail address: fstanczyk@socal.rr.com

1521-690X/$ - see front matter

pilosebaceous unit, which is a common structure in skin that gives rise to hair and sebaceous glands.

Also essential for complete evaluation of the hyperandrogenic patient is knowledgeable use of the clinical laboratory. This requires an appreciation of the diagnostic capabilities and limitations of the wide variety of available laboratory tests. It is essential that relevant and highly reliable tests be used.

The objective of the present chapter is to provide insight into the biochemical aspects pertaining to the diagnosis of hyperandrogenism, particularly in hyperandrogenism associated with hirsutism, acne and alopecia. To this end, the chapter will begin with an overview of what is known about the production, transport, metabolism, and measurement of principal androgens in normal women. This will be followed by a discussion of the structure and physiology of the pilosebaceous unit in skin, and then the biochemistry of androgens in hirsutism, acne and alopecia. In the final part of the chapter, the diagnostic utility of androgenic markers in hyperandrogenic women will be discussed.

OVERVIEW OF PRODUCTION, CIRCULATING LEVELS, TRANSPORT, AND CLEARANCE OF ANDROGENS IN NORMAL WOMEN

Principal androgens

Sources of androgen production in women can be divided into two types: (1) endocrine glands, specifically the adrenals and ovaries; and (2) peripheral (non-endocrine gland) tissues, which can be subdivided into splanchnic and extrasplanchnic sources. Splanchnic sources include the liver and gut, whereas extrasplanchnic sources include a variety of tissues, of which fat and skin make significant contributions. Skin has the largest surface area of any tissue in the body and is an important site of peripheral androgen action.

Five androgens are secreted by the endocrine glands; they include dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione, testosterone, and 5-androstene-3β,17β-diol (androstenediol). The least known of these androgens is androstenediol. This androgen is unique in that it binds not only to the androgen receptor but also to the estrogen receptor.[1] Due to the fact that androstenediol has both androgenic and estrogenic activities, it is sometimes referred to as 'hermaphrodiol'.[1] There is a paucity of data about its physiologic role, and it is rarely measured in clinical diagnostic laboratories. For these reasons, androstenediol will not be discussed further in this chapter. Thus, DHEAS, DHEA, androstenedione and testosterone are considered to be the principal androgens produced by the endocrine glands. Of these androgens, only testosterone is considered to have significant direct androgenic activity. However, the other three androgens are important precursors of testosterone.

In the adrenals and ovaries, DHEA, DHEAS, androstenedione, and testosterone are formed by well-established pathways (Figure 1).[2] Following the formation of pregnenolone and progesterone, these compounds undergo hydroxylation at carbon 17 and subsequent cleavage of the side-chain (carbons 20 and 21), forming DHEA and androstenedione, respectively. 17-Hydroxylation occurs through the action of 17α-hydroxylase, whereas $C_{17,20}$-lyase catalyzes the side-chain cleavage. It is well recognized that both enzymatic activities are catalyzed by a single protein, P450c17, encoded by