Review of Adrenal Androgen Synthesis, Hypersecretion, and Blockade

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KEYWORDS

• Adrenal androgens • Adrenocortical carcinoma • Adrenal androgen blockade
• Metastatic prostate cancer

KEY POINTS

- A series of enzymes derived from the cytochrome p450 superfamily alters the 27-carbon cholesterol molecule to produce several 19-carbon sex hormones known as adrenal androgens.
- Women rely significantly on adrenal androgens throughout development and adulthood, while men have most of their circulating androgens produced by the testes.
- Hypersecretion of androgens stems from a myriad of conditions, all of which can be diagnosed by specific biochemical or imaging-based modalities.
- Malignant adrenal tumors are exceedingly rare, but early identification and diagnosis are imperative as they have an aggressive clinical course.
- Clinical manifestation of androgen deficiency occurs mostly in women, but uniform syndromic characteristics and age-matched levels of baseline hormones are not well defined, making diagnosis challenging.

INTRODUCTION

The adrenal gland is a paired organ that produces several important hormones critical to proper physiologic function. There are 2 anatomically and biochemically distinct regions: the cortex and the medulla.[1] The cortex is separated into 3 zones, which include the zona glomerulosa, the zona fasciculata, and the zona reticularis. The zona reticularis is responsible for the production of 5 19-carbon sex steroids: dehydroepiandrosterone (DHEA), dehydroepiandrosterone-sulfate (DHEAS), androstenedione, androstenediol, and 11β-hydroxyandrostenedione.[1] Here, we review the synthesis of these steroids, their critical function during development and adulthood, and the disorders of hypersecretion and blockade.

HISTORY AND EMBRYOLOGY

The adrenal gland was first mentioned in publication by Bartolomeo Eustachio in the 1500s, in which he described it as "a gland lying on the kidney," but details regarding its function were not well understood.[2] Thought on its role as a hormone-producing organ surfaced initially in 1688, when reports of a virilized, cushingoid 6-year old with an adrenal tumor were first described.[3] In the early 1900s, Bullock and Sequeira depicted the phenotypic presentation that we now understand to be congenital adrenal hyperplasia (CAH). Their findings suggested to scientists at the time that the adrenal glands played a significant role in, at minimum, secondary virilization.[4] Bullock and colleagues was correct, as the

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Abbreviations	
ACC	adrenal cortical carcinoma
ACTH	adrenocorticotrophic hormone
ADT	androgen deprivation therapy
AR	androgen receptor
CAH	congenital adrenal hyperplasia
CRH	corticotropin-releasing hormone
CRPC	castrate-resistant prostate cancer
DES	diethylstilbestrol
DFS	disease-free survival
DHEA	dehydroepiandrosterone
DHEAS	dehydroepiandrosterone-sulfate
DHT	dihydrotestosterone
DZ	definitive zone
FZ	fetal zone
LHRH	luteinizing hormone-releasing hormone
OS	overall survival
PCOS	polycystic ovarian syndrome
PSA	prostate-specific antigen
SIR	severe insulin resistance

5 adrenal carbon steroids do have androgenic activity, and serve as precursors to more potent sex steroids, that is, testosterone and estrogens.[2,5]

In the mid-1900s, new histochemical techniques emerged demonstrating 2 cellularly distinct divisions of the adrenal gland: the cortex and the medulla.[1] The cortex was further delineated into 3 sections known as the zona glomerulosa (mineralocorticoid production), zona fasciculata (cortisol production), and zona reticularis (adrenal androgen production).[1,5,6] Embryologically, the adrenal gland starts as a small clump of mesodermal cells within the urogenital ridge, known as the adrenal-gonadal primordium. These cells eventually give rise to the adrenal cortex at 7 to 8 weeks gestation and are composed of an inner, fetal zone (FZ) and an outer, definitive zone (DZ).[1,5] The FZ produces a large amount of DHEA in response to corticotropin-releasing hormone (CRH) from the placenta, which is used as an estrogen precursor during development.[1,5] After birth, the adrenal gland shrinks to approximately 50% of its size, as the majority of the FZ undergoes apoptosis and the DZ becomes the 3 layers of the adrenal gland in adults.[1] Each layer of the adrenal gland produces a specific hormone, which is derived from cholesterol through a series of enzymatic reactions performed by steroid hydroxylases that belong to the cytochrome P450 superfamily[1,2,5] (Fig. 1).

DISCUSSION

Androgen Synthesis

The production of adrenal androgens begins with cholesterol, which is primarily derived from plasma lipoproteins delivered to the adrenal gland by low-density lipoproteins.[5] Cholesterol is first converted to pregnenolone by cholesterol desmolase, which occurs after the binding of adrenocorticotrophic hormone (ACTH) to adrenal gland receptors (see Fig. 1). This initial cleavage converts the 27-carbon cholesterol molecule into a 21-carbon molecule. The next step involves the enzyme 17α-hydroxylase, forming 17-hydroxypregnenolone, followed by 17,20 Lyase, producing DHEA. The enzyme, cytochrome P450 17A1, derived from the CYP17A1 gene, catalyzes the 17α-hydroxylation reaction, needed for androgen and glucocorticoid creation, and the 17,20 Lyase reaction, necessary for 19-carbon adrenal androgen production.[5,7,8] DHEA is subsequently converted to DHEAS by adrenal sulfokinase or to androstenedione by 3β-hydroxysteroid dehydrogenase. In adults, the sulfation of DHEA acts as a protective mechanism, as excess amounts of DHEA can be converted to testosterone if unregulated.[5,9] Finally, androstenedione is converted to testosterone by 17β-hydroxysteroid dehydrogenase, produced by the AKR1C3 gene, which is the gene largely responsible for the small amount of testosterone produced by the adrenal gland.[5,10] Testosterone is also produced from DHEA, DHEAS, and androstenedione in peripheral tissues, such as hair follicles, sebaceous glands, the prostate, external genitalia, and adipose tissue.[5,11] Testosterone can then be converted to a more potent androgen, dihydrotestosterone (DHT), by 5α-reductase in androgen-sensitive tissues.[5] Peripheral production of testosterone contributes significantly to the overall hormone production in women, but in men, most of the circulating testosterone is produced by the testes. Adipose tissue is largely responsible for the conversion of androstenedione and testosterone to estrone. Estrone can then be reduced to the biologically active estrogen, estradiol, by 17β-hydroxysteroid dehydrogenase.[12,13]

Androgen Secretion and Peripheral Effects

Adrenal androgens and cortisol are secreted synchronously in response to ACTH. The synthesis and secretion of ACTH is regulated by CRH, which is produced in the hypothalamus.[14] Cortisol and androgen production are regulated in 3 ways: circadian rhythm-based episodic secretion, stress response-induced, and direct inhibition of ACTH by circulating cortisol via a negative feedback loop.[5] The majority of the CRH and ACTH is secreted in the sixth to eighth hour of sleep and decreases once wakefulness occurs and the day progresses. If stress responses occur during the day, the production of androgens and cortisol is increased and does not follow circadian rhythmic release.[5] While most adrenal androgens are

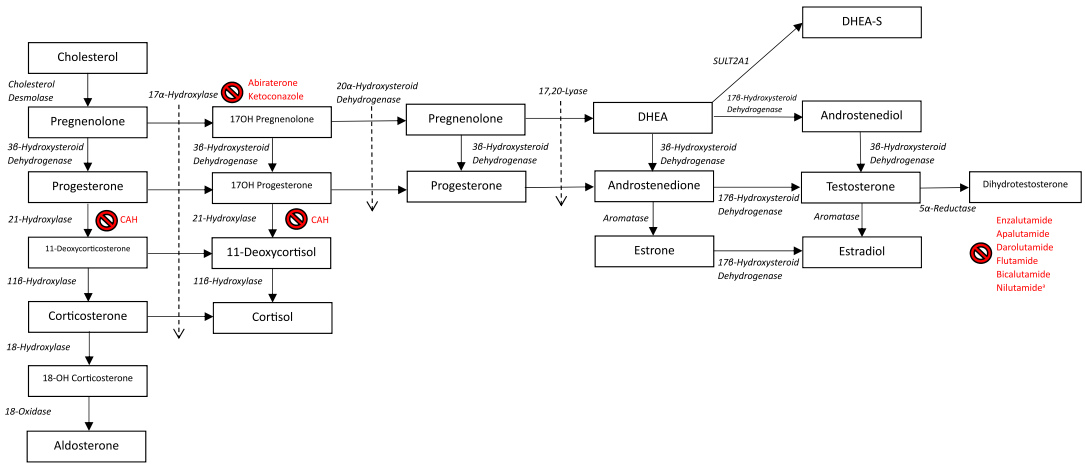

Fig. 1. Adrenal androgen steroid biosynthesis pathway with specific enzymatic blockade produced by conditions/medications. [a]These receptors induce androgen receptor blockade, which are activated by various androgenic molecules (more than solely DHT).

secreted in parallel to cortisol, DHEAS is not, as the circulating half-life is much longer.[15]

There is a transient increase in cortisol synthesis during the 10th week of gestation, potentially exerting a negative feedback loop on ACTH production. Scientists have theorized that this early cortisol production may partially inhibit androgen production, protecting female differentiation during the time of genital differentiation.[16,17] For the first 5 years of life, DHEAS is maintained at minimum concentrations. However, by approximately 6 to 7 years old in females and 7 to 8 years old in males, adrenarche (increased secretion of adrenal androgens) and subsequently, pubarche (appearance of pubic hair) occurs.[5] The increase in DHEAS is the biochemical hallmark of adrenarche, along with the associated axillary and pubic hair growth.

Common Conditions of Adrenal and Nonadrenal Androgen Hypersecretion

Androgen excess is a known disorder in women and is defined as clinical or biomedical evidence of elevate androgenic steroids[18,19] (**Table 1**). Diagnosis is suspected as clinical manifestations arise, and these can be consistent and syndromic. Female patients will commonly present with irregular menstrual cycles, clitoral hypertrophy, external virilization, change in voice, male pattern hair loss, cystic mastitis, and metabolic syndrome.[20,21] Polycystic ovaries are another clinical finding in hyperandrogenic women; a common subtype in this group is hyperandrogenism, insulin resistance, acanthosis nigricans syndrome.[20,22] The most prevalent clinical findings in women overall are hirsutism and acne.[20–23] Diagnosis is harder in men as an increased adrenal sex steroids does not manifest clinically due to their heavier reliance on testes-produced sex hormones. The most prevalent sign in men is gynecomastia, which presents only when there is a high enough peripheral conversion of excess adrenal androgens to estrogen.[21]

Polycystic ovarian syndrome (PCOS) is the most common nontumor-related disorder associated with androgen excess in women with a prevalence of about 10%.[18,24] The majority of PCOS cases are due to increased intraovarian androgen hypersecretion leading to follicular arrest, polycystic ovaries, an-/oligomenorrhea, and hirsutism.[25] However, early literature on PCOS describes a complex interplay of physiologic sources of hyperandrogenism in these patients. Abraham and colleagues evaluated serum steroid levels in 59 hirsute patients after 1 week of dexamethasone suppression, and discovered that nearly 44% of the cohort had adrenal-based hyperandrogenism.[26] Ehrmann and colleagues also described a "functional adrenal hyperandrogenism" subtype among 40 adolescent and adult females with unexplained oligomenorrhea, hirsutism, and acne.[27] Although the majority seemed to have ovarian-specific hypersecretion, 58% of the cohort also demonstrated 17-ketosteroid hyperresponsiveness to a cosyntropin test indicating a primary adrenal or mixed adrenal/ovarian origin of their hyperandrogenic symptoms.[27] While rarer than the "functional ovarian hyperandrogenism" form of PCOS, primary adrenal and mixed adrenal/ovarian subtypes do exist.

CAH is a rare, monogenic form of adrenal androgen excess secondary to (in 95% of cases) a homozygous or compound heterozygous mutation in the CYP21A2 gene on chromosome 6.[18,28]

Table 1
Benign and malignant forms of hyperandrogenism

Common Benign Conditions of Androgen Hypersecretion	Incidence (per year)	Common Symptoms	Diagnostic Testing
Polycystic ovarian syndrome	2%–20% of reproductive age women	Hirsutism, acne, alopecia, clitoromegaly, menstrual irregularities, metabolic syndrome	Serum total testosterone, 17-hydroxyprogesterone (early follicular phase), hCG, TSH, FSH, AMH, transvaginal ultrasound
Congenital adrenal hyperplasia	1 in 15,000 births	Ambiguous genitalia ± adrenal crisis/ salt wasting, early pubarche	17-hydroxyprogesterone, cortisol, serum electrolytes
Severe insulin resistance syndrome	–[a]	Acanthosis nigricans, hirsutism, ovarian dysfunction, menstrual irregularities	Fasting glucose, fasting insulin, oral glucose tolerance test, c-peptide, leptin
Cushing's syndrome	6.2–7.6 per 1 million patients[b]	Proximal muscle weakness, facial plethora, peripheral wasting, abdominal striae, bruising, menstrual irregularities[c]	Bedtime salivary cortisol, 24-h urinary cortisol, dexamethasone suppression test
Ovarian hyperthecosis	–[a]	Acne, hirsutism—early Hair loss, clitoromegaly, low voice, obesity—later	Testosterone, LH, FSH, lipid profile
Androgen-secreting adrenal adenoma	0.1%–1.7% of patients with adrenal tumors	Hirsutism, virilization, abdominal fullness, satiety	Testosterone, DHEAS, DHEA, androstenedione, cortisol, plasma/ urine metanephrines, aldosterone, aldosterone/renin ratio
Malignant conditions of androgen hypersecretion			
Virilizing ovarian tumor	3.7 per million—germ cell 2.1 per million—sex cord stromal	Precocious puberty, uterine bleeding, menstrual irregularities, hirsutism, virilization clitoromegaly	Testosterone, DHEA, 17-OHP, transvaginal ultrasound
Adrenocortical carcinoma	1–2 per million patients	Hirsutism, virilization, abdominal fullness, satiety	Testosterone, DHEAS, DHEA, androstenedione, cortisol, plasma/ urine metanephrines, aldosterone, aldosterone/renin ratio

Abbreviations: 17-OHP, 17-hydroxyprogesterone; AMH, anti-Mullerian hormone; FSH, follicle stimulating hormone; hCG, human chorionic gonadotropin; LH, leuteinizing hormone; TSH, thyroid stimulating hormone

[a] No uniform data available.

[b] Incidence for Cushing's disease.

[c] Symptoms associated with hyperandrogenic symptoms also occur as previously described.

The mutation leads to dysfunction of the 21-hydroxylase enzyme preventing the conversion of 17-hydroxyprogesterone to 11-deoxycortisol.[28] This results in an overproduction of ACTH, leading to an increase in adrenal androgens and a deficiency in glucocorticoids and mineralocorticoids.[28] In female neonates, ambiguous genitalia are usually the presenting abnormality, while male infants are detected around 2 to 4 weeks with salt-wasting adrenal crises.[18,28] Nonclassic CAH is characterized by partial function of the 21-hydroxylase enzyme with some production of mineralocorticoids and glucocorticoids, resulting in a lower incidence of salt-wasting and adrenal insufficiency.[18]

Women with androgen excess in reproductive ages can harbor a syndrome of severe insulin resistance (SIR).[29] SIR syndromes are due to either a primary mutation in insulin receptor genes or primary adipose tissue dysfunction, such as lipodystrophy.[18] The high levels of circulating insulin can act synergistically with luteinizing hormone producing a consistent surge of androgen production.[18] SIR can mimic PCOS in several ways including ovarian cysts on ultrasound and menstrual irregularities, however, high fasting serum insulin levels, presence of acanthosis nigricans, a strong family history of diabetes, and a normal body mass index (BMI) can delineate the etiology.[18] Further, in contrast to adrenal tumor-based forms of androgen excess, serum testosterone is significantly elevated (>10 nmol/L) in SIR syndromes.[18]

Less common causes of androgen excess also include Cushing's disease, ovarian hyperthecosis, and virilizing ovarian tumors. Cushing's disease accounts for 1% and 4% of adrenal hypersecretion in premenopausal and postmenopausal women, respectively.[30] Typical syndromic findings associated with Cushing's disease delineate this pathology from other causes and it has a much more indolent course when compared with tumor-based secretion. Ovarian hyperthecosis results from excess androgen production in ovarian stromal cells and is the result of a complex interplay between insulin resistance, pituitary LH secretion, and stromal hyperproliferation.[18,31] Virilizing ovarian tumors have a rapid clinical course with severe virilization and significantly elevated levels of testosterone (~20 nmol/L).[18,32,33] They account for 5% of all ovarian tumors and early diagnosis is imperative to optimize outcomes in the setting of malignant lesions.[18]

Purely androgen-secreting adrenal tumors (aspartate aminotransferase [AST]) are a rare finding in both children and adults.[34] In several studies analyzing over 1200 patients with adrenal tumors, the rate of AST was 0.1% to 1.7%.[30,35] Nonetheless, there is a small, but important, population of patients with this disease. Liao and colleagues performed a systematic review of pure AST and found that approximately 72% and 26% of tumors demonstrated benign or malignant biologic activity, with the remaining having uncertain biologic behavior.[21] Further, they discussed that testosterone and DHEAS were the most commonly elevated androgens in AST (with higher values in malignant tumors). In earlier studies, urinary 17-ketosteroid levels were also an indicator of hyperandrogenism.[21] The peak age range for benign AST occurred around 21 to 30 years of age, which may be secondary to young female patients noticing symptoms of hirsutism more readily than male age-matched counterparts.[21] Malignant AST occurred at 41 to 50 years of age, a common age range for diagnosis of adrenocortical carcinoma.[21,36,37] Typically, benign AST are also smaller in size (5 cm vs 9 cm) and the time to diagnosis (4.5 years vs 2 years) is longer when compared with malignant AST, likely due to the more aggressive progression of malignant tumors.

Hypersecretion in Adrenal Cortical Carcinoma

Adrenocortical carcinoma's are rare, lethal malignancies representing just ~300 cases and 0.2% of deaths annually in the United States[38,39] (**Fig. 2**). There is a bimodal age distribution, occurring more in children less than 5 years old and in adults aged 40 to 60 years old.[38] They can occur in the setting of genetic syndromes including Li-Fraumeni, Beckwith-Wiedemann, Neurofibromatosis-1, Carney Complex, Werner, Familial Adenomatous Polyposis, Multiple Endocrine Neoplasia Type I, and Lynch Syndrome.[40,41]

Most patients present with symptoms of hormonal excess (40%–60%), with the remaining

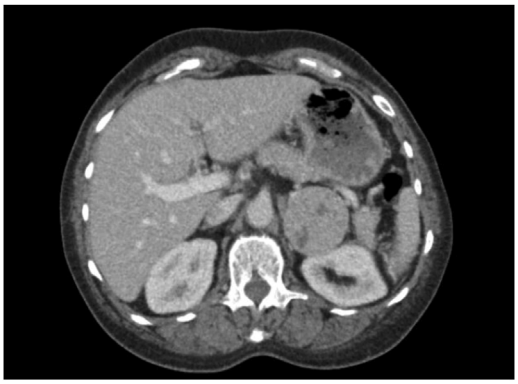

Fig. 2. A 69-year-old female with an incidentally detected left adrenal mass. Diagnosis was primary ACC following complete resection.

demonstrating symptoms of tumor growth (abdominal pain, abdominal fullness, early satiety)[38,41] (see Table 1). Patients who are not symptomatic typically have their diagnosis discovered on incidental imaging (20%–30%) and demonstrate advanced tumor characteristics (average tumor size 10–13 cm)[38,41,42] (see Fig. 2). Hypercortisolism, evident in patients with plethora, diabetes mellitus, osteoporosis, and muscle atrophy, is the most common form of hormonal hypersecretion in adrenal cortical carcinoma (ACC).[38,43] Hyperandrogenism is the second most common hormonal disturbance with symptoms of male pattern baldness, virilization, hirsutism, and menstrual abnormalities. About 1% to 3% will have increased estrogen production resulting in gynecomastia and testicular atrophy.[38] Rarely, glucocorticoid-mediated hypersaturation of the hydroxysteroid dehydrogenase-11β-2 enzyme receptors will lead to excess mineralocorticoid production leading to hypertension and hypokalemia.[38,43]

Biochemical testing can be useful in narrowing the differential diagnosis for patients suspected of having ACC. American Association of Endocrinologist and American Association of Endocrine Surgeon's recommend a biochemical workup for all patients with an adrenal incidentaloma.[44] This includes an overnight 1-mg dexamethasone suppression test, midnight salivary cortisol or a 24-hour urine cortisol to rule out cortisol-producing lesions. Plasma aldosterone, renin, and an aldosterone/renin ratio should be obtained to identify aldosterone producing tumors. Pheochromocytoma is evaluated by measuring plasma or 24-urine metanephrines/normetanephrines. Finally, androgen-producing masses are investigated by obtaining serum DHEAS, androstenedione, and free testosterone levels.[38,43–45] Hyperandrogenism secondary to ACC typically demonstrates higher levels of free testosterone when compared with most nontumor-related hypersecretion. In a retrospective analysis of patients with adrenal producing tumors, a free testosterone level greater than 8.85 pg/mL demonstrated a sensitivity of 82% and a specificity of 97% for diagnosis of ACC.[45] The authors mention, however, that there is significant overlap in tumor-mediated and nontumor-mediated hyperandrogenism, and imaging should play an important diagnostic role.

A multicenter trial evaluated the prognostic association of hormone secretion type for patients with adrenocortical carcinoma.[46] Eight hundred seven patients with cortisol-secreting, mixed cortisol/androgen secreting, androgen-secreting, and nonhormone secreting ACC were compared regarding disease-free survival (DFS) and overall survival (OS). DFS and OS for the entire cohort were poor, at 9 and 60 months, respectively, highlighting the aggressiveness of the tumor. Median DFS was 7 months, 8 months, 10 months, and 12 months for cortisol-secreting, mixed cortisol/androgen secreting, androgen-secreting, and nonhormone secreting, respectively. OS was 36 months for cortisol-producing, 30 for mixed, 60 months for androgen producing, and 115 months for nonhormone producing ACC [$P \leq .05$]. On multivariate analysis, mixed-secreting ACC was an independent risk factor for worse OS; however, this included patients with positive surgical margins (which was also an independent risk factor). In a subgroup, multivariate analysis of patients with negative tumor margins, cortisol-producing tumors were an independent risk factor for worse DFS.[46] A follow-up meta-analysis investigated the same clinical endpoints in patients with ACC and varying forms of hormonal secretion. Among ~3800 patients with ACC, cortisol-producing tumors demonstrated the worst OS and DFS (risk ratio RR 1.43, [95% CI 1.18–1.73]). Androgen-producing tumors were not overtly associated with survival endpoints.[47]

Confirmation of ACC involves a myriad of variables identified on cross-sectional imaging (CT). Traditionally, masses $\geq$ 4 cm are deemed high risk for malignancy and a small minority of patients with ACC have masses less than 6 cm, with 3% found to be 4 cm or less.[38,41,42] Further, ACC tends to have an irregular, heterogenous shape, and may frequently have central areas of necrosis or calcification.[38,48] A prospective, multi-institutional study found that using an unenhanced CT, tumor detection cut-off of greater than 20 HU, tumor size $\geq$ 4 cm, and positive urine steroid metabolomics produced a positive predictive value of 76.4% and negative predictive value of 99.7% for the detection of ACC.[49] Further, there are data demonstrating size may have a prognostic value, as patient's with smaller tumor size (<5 cm) may have improved OS when compared with patients with more advanced tumors.[50]

Androgen Deficiency

Adrenal androgen deficiency is a contested topic that exists almost exclusively in the female population. Adrenal androgen deficiency in males would likely go unnoticed due to the maintenance of circulating sex hormones produced by the testes. More commonly, in males and females, patients will suffer from adrenal insufficiency, which can be primary (adrenal gland failure), secondary (failure of pituitary ACTH production), or tertiary (lack of CRH from the hypothalamus).[51] Adrenal failure presents as a spectrum of clinical manifestations, from mild

symptoms to life-threatening shock. Patients with adrenal failure will usually have decreased production of mineralocorticoids, cortisol, and adrenal sex hormones (with the exception of secondary and tertiary adrenal failure where mineralocorticoid production is preserved).[51]

Sex hormones in women are produced in the adrenal gland, ovary, and from peripheral conversion of prohormones in various areas of the body. The only androgen solely produced by the adrenal gland is DHEAS, which is the most abundant androgen in the body.[52] In general, serum androgen concentrations naturally decline with age and plateau when a woman reaches menopause.[53,54] When a woman reaches 70 years old, serum concentrations of androgens are 20% of those in a 20-year old.[53] Outside of natural age-based decline, there are several conditions suggested to cause androgen deficiency in women: bilateral oophorectomy, primary adrenal insufficiency, hypopituitarism, anorexia nervosa, medications (oral contraceptives, glucocorticoids), and human immunodeficiency virus.[52]

Androgen deficiency in females, termed androgen deficiency syndrome, is a controversial term as the Endocrine Society Clinical Practice Guidelines suggests against formalizing the diagnosis. They state that there is a lack of well-defined clinical characteristics corresponding with a syndrome as well as age-based normative data for serum testosterone and free testosterone concentrations.[55] Nonetheless, there are several proposed side effects of androgen deficiency in women including: impaired follicular development, poor sexual function, low bone mineral density, and changes in mood or cognitive function.[52,56,57] Interestingly, in one series of women with hypopituitarism and associated adrenal deficiency, sexual function did not show improvement until testosterone concentration reaches the upper limit of normal.[58] Further, sexual dysfunction among hyperandrogenic conditions may vary, as women with PCOS do not display signs of hypersexuality, however, some reports have demonstrated intrusive sexual thoughts in women with androgen-secreting tumors.[52]

Overall, primary adrenal androgen deficiency is a rare finding in both men and women with most patients suffering from complete adrenal insufficiency. Decreased androgen production in females remains a controversial topic with most clinicians declining to recognize this as a formal diagnosis.

Blockade of Adrenal Androgens in Men with Prostate Cancer

Androgen blockade in the setting of prostate cancer dates back to 1941 when a landmark publication from Dr Charles B. Huggins demonstrated that bilateral orchiectomy produced a significant drop in serum acid phosphate levels. Further, patients injected with testosterone displayed increased levels of serum phosphatase, leading to the notion that prostate cancer was fueled by androgen production in men.[59] Diethylstilbestrol (DES), an estrogenic compound, was also introduced for medical use around the same time (1938) and was quickly discovered as a potent androgen blocker (via negative feedback on the hypothalamus).[60] In the early 1970s, Schally and colleagues developed a purified form of luteinizing hormone-releasing hormone (LHRH) called leuprolide, which was followed by the discovery that LHRH receptor agonism led to receptor downregulation and subsequent medical castration.[59] Leuprolide became the first Food and Drug Administration (FDA)-approved LHRH agonist for the treatment of prostate cancer, and in a randomized study comparing testosterone levels after leuprolide or DES, leuprolide produced equivalent castration without the cardiovascular side effects that plagued DES.[61]

LHRH agonists exploded onto the market, and with a minor alternation in the sixth amino acid of the molecule, alternate forms of LHRH agonists were introduced, differing solely in their mode of administration (intramuscular, subcutaneous, subcutaneous implant).[59] However, the issue of "testosterone flare" soon became an issue, that is, the sudden increase in testosterone with initial administration of an LHRH agonist. This was thought to produce a tumor flare and the potential for worse disease-specific outcomes.[62,63] The "tumor flare" concerns led to the development of a new class of antiandrogens: the LHRH antagonists. The LHRH antagonists rapidly produce castrate levels of testosterone, without the "flare" associated with LHRH agonists, and in a meta-analysis of randomized trials comparing LHRH agonists to antagonists, they were found to have a lower rate of all-cause mortality and cardiovascular side effects.[59,64] In the same study, however, there was no difference in prostate cancer-specific outcomes, musculoskeletal events, or other serious adverse effects.[64]

While the antiandrogen effect of both agents was proven to be extremely effective for prostate cancer treatment, the side effects of androgen blockade is extensive. Most common adverse effects include hot flashes, fatigue, sexual/erectile dysfunction, testicular atrophy, cognitive decline, cardiovascular events, and decreased bone mineral density. In fact, the American Urological Association/Society of Urologic Oncology (AUA/SUO) guidelines on advanced prostate cancer recommend preventative treatment of skeletal-related

events including calcium, vitamin D, smoking cessation, and weight-bearing exercise. In those with castrate-resistant prostate cancer (CRPC), bone-protective agents (denosumab or zoledronate) are recommended.[65]

In men with nonmetastatic disease who want to limit the sexual side effects associated with LHRH agonists/antagonists, androgen receptor (AR) blockers are an option. These agents block the binding of DHT to the AR without reducing serum levels of testosterone. Typically, however, patients may start with an AR blocker with eventual use in combination with LHRH agonists/antagonists as a form of dual androgen blockade and are particularly useful in the initiation of hormone therapy to prevent the previously mentioned testosterone surge.[59,66]

While all patients initially respond to castration, resistance to androgen blockade is an inevitable progression. Eventually, the AR pathway is reactivated and no longer relies on the androgen production by the testes.[59] There are a number of mechanisms of castrate resistance that have been proposed in the literature (the extent of which are outside the scope of this review), including AR amplification and AR mutations leading to activation of the AR by nonandrogenic molecules.[67] In the presence of androgen deprivation therapy (ADT), circulating androgen levels are extremely low, however, analysis of intratumoral levels of androgens have been found to be the same or even higher than in eugonadal men.[68] This is believed to be, in part, due to an adrenal production of DHEA and DHEAS, which is converted to DHT through a "back-door" pathway known as the 5α-dione pathway.[69] Further, CRPC cells induce production of altered steroidogenic enzymes that allow tumor cells to biosynthesis androgens from available adrenal androgenic precursors such as DHEA or androstenediol.[70] High concentrations of androstenediol have been demonstrated in prostate cancer cells even after use of ADT.[71] In this setting, androstenediol acted as a potent activator of mutant AR's, leading to increased cell proliferation, prostate-specific antigen (PSA) mRNA expression, and PSA promotion than DHT.[71] Therefore, the notion that adrenal androgens are a significant contributor to the castrate resistance mechanism in prostate cancer is widely accepted.

In response, several third-generation antiandrogens were developed as a means of performing a complete androgen blockade, that is, both testicular and adrenal sources of androgen production are halted. This included abiraterone which inhibits androgen production from all sources (adrenal, testis, and prostate), by selectively and irreversibly inhibiting the enzyme 17α-hydroxylase.[59] Apalutamide and enzalutamide both bind to the AR, limiting AR-mediated nuclear translocation, interaction and activation of resistant tumor-associated androgen genes, and, overall, the prostate cancer-stimulating effect of testicular and extragonadal (adrenal) sources of androgens.[59]

Historically, an antifungal medication called ketoconazole, a nonselective 17α-hydroxylase inhibitor, has been used off-label for castrate-resistant prostate cancer.[72] While it is effective in inhibiting the production of testosterone, androstenedione, DHEA, and DHEAS, it has yet to demonstrate survival benefits and has given way to more modern hormone therapies such as abiraterone.[72] Ketoconazole is, however, cheaper, has a faster onset of action, and possibly less side effects than traditional hormone therapy.

Androgen deprivation has progressed drastically since the introduction of bilateral orchiectomy in the 1940s. Since that time, a variety of androgen deprivation therapies have been developed as our knowledge of prostate cancer biosynthetic mechanisms have grown. It has become clear that prostate cancer cells rely not only on gonadal sources of androgen production but also on extra-gonadal sources, particularly the adrenal gland. In fact, the current first-line therapy for metastatic prostate cancer includes ADT in combination with an agent for adrenal androgen blockade.

SUMMARY

Adrenal androgens serve an important role in the biochemical function of the adrenal cortex. There are several important enzymatic steps that convert the 27-carbon cholesterol molecule into the 19-carbon sex hormones that are eventually released into the blood stream. There is a myriad of conditions that result in hyperandrogenic states, and comprehensive history-taking, biochemical testing, and imaging help to narrow the diagnosis. Androgen-secreting adrenal tumors are rare, and care should be taken to identify malignant lesions as they portend a poor prognosis without treatment. Adrenal deficiency effects mostly women, but currently there is no clinical criteria or consensus treatment due to the lack of uniform syndromic findings or age-matched baseline hormone levels. Blockade of adrenal androgens has become a cornerstone of treatment of men with metastatic prostate cancer.

CLINICS CARE POINTS

- Androgen excess is characterized by male pattern hair loss, hirsutism, voice changes (deepening voice), acne, amenorrhea.

- Androgen excess is more difficult to diagnose in men due to high levels of innate circulating testosterone produced by the testes.
- Androgen excess may occur in adrenal disorders (eg, adrenocortical carcinoma, adrenal adenoma, congenital adrenal hyperplasia), polycystic ovarian syndrome, ovarian tumors.
- Recently, blockade of adrenal androgen production has been targeted by drugs and utilized in the treatment of advanced prostate cancer.

DISCLOSURE

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