TABLE 2.

Observations Related to Androgen Physiology in Acne Vulgaris Including Gender-Associated Characteristics
Acne-affected skin produces higher levels of T and DHT than in healthy individuals
Conversion of T to DHT is 30-fold higher in AV-affected skin compared to normal skin
Androgen stimulation of sebocyte proliferation is greatest in facial skin
Serum levels of DHEA-S at onset of AV in preadolescent girls are an accurate predictor of the potential for greater AV severity in the future
DHT has been shown to increase sebum production and pro-inflammatory cytokine production by sebocytes
Increased reduction activity of 17β-HSD is indicative of increased local T synthesis in sebaceous glands from AV-affected skin as compared to normal skin
17β-HSD isoforms that convert androstenedione to T are preferentially expressed on facial sebaceous glands
Sebum production increases at puberty and is greater overall in males compared to females
Increased DHT and 3-α-androstanediol glucuronide plasma levels are often found in females with AV whereas DHEA-S, T, and androstenedione are within normal limits

Key: T, testosterone; DHT, dihydrotestosterone; AV, acne vulgaris; DHEA-S, dehydroepiandrosterone sulfate; 17β-HSD, 17β-hydroxysteroid dehydrogenase.
References: 1,3,8

The development of AV correlates directly with the emergence of puberty which is associated with increased androgen levels and production of sebum.[1-4,8] Sebum, an admixture of triglycerides, diglycerides, wax esters, squalene, cholesterol, and sterol esters, is produced by sebocytes, with some contribution by lipases produced by commensal bacteria (*Cutibacterium acnes* [formerly *Propionibacterium acnes*]) within the follicular canal, which hydrolyze triglycerides to free fatty acids (FFA).[3,5] Sebum production varies among individuals and races, and from the end of puberty remains relatively constant through mid-adulthood, followed by a decline in both genders later in life.[3] In addition, androgen (ie, DHT) stimulation also appears to contribute to lipogenic differentiation by functional AR-expressive sebocytes and can increase both sebum production and pro-inflammatory cytokine production by sebocytes.[1,16] It is also recognized that sebaceous glands and sebum play a role in innate immunity and antimicrobial defense.[3,5,8] Sebaceous glands/sebocytes express certain pattern recognition receptors (ie, Toll-like receptors) involved in cutaneous innate immune defense.[5] Several antimicrobial peptides (ie, cathelicidins, defensins, psoriasin) are expressed within sebaceous glands, and FFAs in sebum are active against gram-positive bacteria via upregulation of β-defensin-2 expression.[5,17,18]

Although increased androgens and sebum contribute to AV development, presence of sebum alone is not sufficient to induce AV.[3] Overall, AV is associated with larger sebaceous glands and higher sebum production.[3] Sebum in individuals with AV is similar overall in composition to sebum from non-acne affected skin, but with higher levels of squalene monosaturated FAs and less linoleic acid.[8] A major role of sebum in AV pathophysiology is to provide a follicular microenvironment and nutrient source for *C acnes* proliferation within the pilosebaceous unit which stimulates innate immune response and pro-inflammatory cytokine production by sebocytes, keratinocytes, and perifollicular monocytes.[1,8] *C acnes* lipases also convert sebum triglycerides and diglycerides into FFAs which may promote follicular keratinization and stimulate chemotaxis.[3,8] Inhibition of androgen stimulation that augments sebaceous gland proliferation and sebum production can produce downstream therapeutic benefit by reducing the microenvironment conducive to *C acnes*-related activity in AV.

Androgen Physiology, Androgen Receptors, and Cutaneous Diseases Including Impact of Gender and Ethnicity/Race

The close interplay that circulating androgens, local tissue androgen production/ degradation, and AR functionality have with sebaceous gland activity and sebum production can play a major role in AV pathophysiology, especially when genetic polymorphisms and AR dysfunctions occur. In fact, aberrations in sex hormone physiology, AR genetic polymorphisms, and/or enzymatic abnormalities have been shown to be associated with a variety of systemic diseases (ie obesity, diabetes, prostate cancer, male infertility) and cutaneous diseases (ie AV, AGA, hirsutism, hidradenitis suppurativa).[1,2,13,14,19] With regard to cutaneous disease states, AV is the focus of discussion in this manuscript, however, the roles of androgens and AR functionality in other cutaneous diseases have been reviewed elsewhere.[1,2,13]

Several observations have been associated with androgen-related physiology including gender-related characteristics. Table 2 depicts important observations related to androgen activity and also gender-related factors.

Ethnic/racial variations in physiologic responses, enzyme function, chemical/drug metabolism, and disease propensities are well recognized. These differences appear to occur due to genetic polymorphisms, tissue receptor functionality and distribution, tissue enzyme activity and distribution, circulating hormone levels, and environmental/exogenous factors.[19]

Within the normal range of AR CAG repeat chain lengths, ethnic differences have been observed in healthy men. The

mean number of AR CAG repeat chain lengths is reported to be shortest for men of African descent (≤18--20), followed by Caucasian men (21--22), and with the longest AR CAG repeat chain lengths noted in East Asian men (22-23).[6] As noted above, shorter AR CAG repeat chain lengths correlate directly with increased AR transcriptional activity in both normal skin and in association with disease states.[6,7,13,14] Table 3 reviews important observations related to genetic and ethnic variations in androgen receptors and androgen physiology.

Modulation of Androgen Physiology and Therapeutic Interventions in Acne Vulgaris

Despite the central importance of androgens and sebaceous gland activity in the pathophysiology of AV, the availability of therapeutic agents that modulate androgen physiology and AR activity has been relatively limited.[4,8,20,21] In the United States (US), the two major approaches have been systemic (oral) therapy with spironolactone (not Food and Drug Administration [FDA]-approved for AV), combination oral contraceptives

TABLE 3.

Observations Related to Genetic and Ethnic Variations in Androgen Receptors and Androgen Physiology
Levels of DHT reported to be lower in Asian men compared to white men and black men
Differences between T production in Asian men and white men when Asian men studied in country of origin but not when both groups studied within the US
After correction for comorbid factors and BMI in men (N>500), black males had significantly higher DHT levels and DHT to T conversion ratios than white men and Hispanic men, but no differences in serum T, DHEA-S, and SHBG levels
After correction for comorbid factors, age and BMI in men (N=1413), serum T levels were similar in non-Hispanic white men (n=674), non-Hispanic black men (n=363) and Mexican-Asian men (n=376) with levels higher in the latter group after adjustment for percent body fat; SHBG levels were similar among all groups after adjustment for percent body fat
Longer AR CAG repeat chain lengths correlate with lower AR transcriptional activity in both normal skin and in disease states
Low fat diet shown to decrease serum and urinary androgens, T production rates and serum estradiol levels in healthy men
Polymorphisms of 5α-reductase and aromatase exist but are poorly studied
Coactivators and corepressors of steroid hormone receptors vary in different tissues and require additional research

Key: DHT, dihydrotestosterone; BMI, body mass index; AR, androgen receptor; CAG, cytosine-adenine-guanine; T, testosterone; DHEA-S, dehydroepiandrosterone sulfate; SHBG, sex hormone binding globulin.
References: 6,7,13,14,19

TABLE 4.

Therapeutic Approaches Currently Available or in Development in The United States for Acne Vulgaris that Exhibit Anti-Androgenic Properties	
Agent	**Pharmacologic/Therapeutic Activity**
Oral Agent	
Combination Oral Contraceptives	• Contain ethinyl estradiol and a progestin • Type of progestin affects interactions with AR and other hormone receptors and the relative magnitude of androgenic or anti-androgenic effects • Block ovarian androgen production through suppression of gonadotropins (FSH, LH) • Ethinyl estradiol increases SHBG which decreases free T levels, reduced T binding to AR, and lower conversion of T to DHT • Demonstrated equivalent efficacy in AV lesion reduction to oral antibiotics after 6 months duration of therapy
Spironolactone	• Supported by widespread anecdotal use and available literature for treatment of AV, hirsutism, and AGA • Inhibition of sebaceous gland activity with 30%-75% dose-dependent reduction in sebum excretion • Reduce 5α-reductase activity with increased T clearance via augmented liver hydroxylase activity • Decreased circulating free testosterone via increase in SHBG
Flutamide	• Non-steroidal androgen receptor blocker (approved for therapy of prostate cancer) that may effectively treat AV, AGA, and hirsutism • Active metabolite (2-hydroxyflutamide) a potent competitive inhibitor of DHT binding to AR • Usage limited by hepatic and hematological adverse effects and absolute need to avoid during pregnancy (male fetus pseudo-hermaphroditism)
Topcal Agents	
Clascoterone	• NDA submitted to FDA for approval • Also referred to as cortexolone 17β propionate • Efficacy and safety evaluated in pivotal trials • AR inhibition with suppression of AR-mediated transcription • Reduced lipid and inflammatory cytokine synthesis by sebocytes

Key: AR, androgen receptor; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone binding globulin; T, testosterone; DHT, dihydrotestosterone; AV, acne vulgaris; AGA, androgenetic alopecia; NDA, new drug application.
References: 4,8,20-30

(some agents FDA-approved for AV), or combination therapy using both agents.[4,8,20-27] In the US, use of oral flutamide (not FDA-approved for AV), a competitive inhibitor of AR binding by DHT, has been reported; its use has been limited primarily due to adverse effects and pregnancy-related concerns.[4,8,20] In Europe and Canada, cyproterone acetate has long been used as both an oral antiandrogen and progestin that exhibits marked efficacy for AV both as monotherapy and in combination with estrogen as an oral contraceptive, however, it is not available in the US.[4,8,20,21]

At present, topical antiandrogen therapy is not available. However, topical clascoterone (cortexolone 17α propionate), an AR inhibitor, has completed the formal drug development process and has been submitted to the FDA to be evaluated for approval for treatment of AV.[28-30] Clascoterone has been shown to bind the androgen receptor (AR) with high affinity in vitro, inhibit AR-regulated transcription, and antagonize androgen-mediated lipid and inflammatory cytokine production in human sebocytes, with a greater ability to inhibit inflammatory cytokine synthesis from sebocytes when compared to spironolactone.[28] These research findings reported with clascoterone further support the significance of direct inhibition of AR in the management of AV, with potential application for other androgen mediated skin disorders.

CONCLUDING REMARKS

Advances in understanding of androgen physiology including both central and local tissue mechanisms, enzymatic functions that modulate androgen synthesis and degradation, and AR functionality including the impact of genetic polymorphisms have furthered our understanding of androgen-related diseases states and potential therapeutic options. The above, coupled with increased understanding of receptors and pathways that modulate sebaceous gland activities has also expanded our perspectives on potential therapies for AV. Further elucidation of the functions of androgens and androgen receptors in specific skin disorders can help to shift our focus to the development of therapies that selectively target AR and other receptor pathways that can effectively modify disease and hopefully reduce the risk of adverse effects.

DISCLOSURES

Dr. Del Rosso has served as an advisory board member for Cassiopea, Inc. Dr. Kircik has served as an advisory board member and a consultant for Cassiopea, Inc. Dr. Stein Gold has served as a research investigator and advisor for Cassiopea Inc. Dr. Thiboutot has served as a research investigator and advisory board member for Cassiopea Inc.

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