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 ORIGINAL ARTICLE

New Insights Into Systemic Drivers of Inflammation and Their Contributions to the Pathophysiology of Acne

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ABSTRACT

Acne Vulgaris (AV) is a prominent skin disease commonly affecting teenagers. It often persists into adulthood and is associated with adverse physical and psychosocial impacts. The pathophysiology of AV is conventionally correlated with 4 factors within and around the pilosebaceous unit: increased sebum production, follicular hyperkeratinization, *Cutibacterium acnes* proliferation, and localized immune responses. As such, conventional therapeutic approaches for AV have primarily focused on these factors. In addition to this primarily localized pathophysiology, there is a progressively emerging body of evidence indicating that underlying systemic factors contributing to a generalized immuno-inflammatory response can contribute to or exacerbate AV. In this article, we introduce and provide the supporting data, for 6 patient-centric systems that may be implicated in the development of AV: psycho-emotional stress, diet and metabolism, dysbiosis of the gut and skin microbiome, hormonal fluctuations, oxidative stress, and immune response. Identifying these pathways and their contributions in a patient-centric approach may provide expanded therapeutic opportunities for treating patients with AV.

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INTRODUCTION

Acne vulgaris (AV) is the eighth most prevalent disease globally, and a condition reported to affect at least 50 million people in the United States.[1] Because AV affects 80% of teenagers, it is generally categorized as a condition of adolescence, yet recent literature indicates that AV can affect both pre-teens and adults, with 40%-50% of women experiencing AV that occurs past the teenage years.[2-4] Physical and psychosocial sequelae associated with AV include dyschromia, scarring, poor self-image, depression, anxiety, and avoidance of social interaction.[5,6]

The pathophysiology of AV is conventionally viewed as resulting from 4 factors occurring at the pilosebaceous unit (PSU): increased sebum, follicular hyperkeratinization, proliferation of *Cutibacterium acnes*, and inflammation induced by localized immune responses.[5] Collectively, this sequence of pathophysiologic events causes marked inflammation in and around the PSU, which results in visible AV lesions and can ultimately lead to both persistent and post-inflammatory hyperpigmentation (PIH) and/or post-inflammatory erythema (PIE) and various forms of scarring.[7]

However, there is emerging evidence that many dermatologic conditions are associated with generalized underlying immune-inflammatory systemic responses. Psoriasis, once viewed and treated only as a skin disease, is now accepted as a systemic, inflammatory disease managed primarily by immunomodulatory therapies.[8] Atopic dermatitis is now approached, based on scientific evidence, as a disorder driven by a variety of pathways of inflammation, both systemic and cutaneous.[9] Hair loss and thinning, once thought of as primarily having local pathogenesis, is now accepted as a multi-factorial systemic condition with more similarities than differences across the hair loss disorder spectrum.[10]

Likewise, evidence now suggests that the localized pathophysiology of AV is not an isolated event but may be induced or exacerbated by an interconnected web of external and internal stressors propagated by various inflammatory signaling pathways.[5] Therefore, an important question to address is what systemic drivers are likely to directly contribute to the pathophysiologic development of AV occurring within and around the PSU. If we can address this question, we might then develop and provide a wider range of therapeutic options.

In this article, we use a systems-wide perspective to identify 6 relevant associations serving as contributory factors of systemic inflammation that may promote the development and/or augment the severity of AV. These include psycho-emotional stress, an unbalanced diet and metabolism, dysbiosis of the gut and skin microbiome, hormonal fluctuations, oxidative stress, and immune response. Many of these factors have long been cited as playing a role in AV through personal observation or case reports. Presently, clinical and mechanistic evidence suggests the involvement of these factors in the pathophysiology and severity of AV.[5,11] Below, we review the current literature supporting these systemic stressors and how they may drive AV lesion formation.

MATERIALS AND METHODS

Systems-Wide Pathophysiology of Acne Vulgaris

The pathophysiology of AV, whether talking about local or systemic cascades that contribute to AV lesion formation or their sequelae, begins and ends with the presence of inflammation, which is subclinical prior to the onset and after the visible resolution of active (palpable) AV lesions.[5,12] Our conventional approach to AV management, whether using topical and/or systemic medications, has been to target the 4 major pathophysiologic mechanisms that correlate with the development of AV lesions: follicular hyperkeratosis (microcomedo formation), *C. acnes* proliferation, increased sebum, and inflammation resulting from local immune responses.[12] Over time, publications on AV added to the importance of skin care and exogenous agents, and in more recent years, other considerations such as diet and the microbiome have emerged in the literature.[13-17]

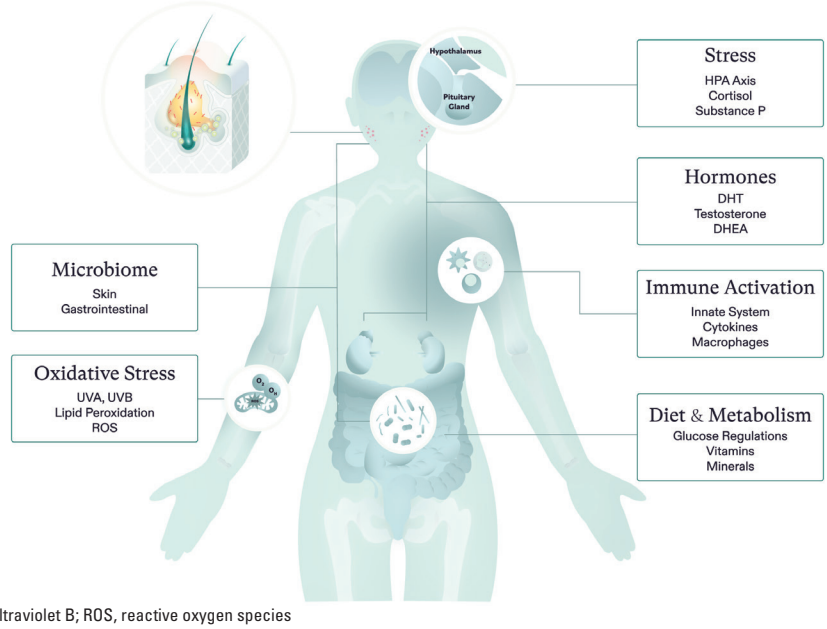
From the time benzoyl peroxide was discovered for AV in the 1960s, we had little information beyond data on how medications for AV worked until more recently.[18] In addition, more attention is being paid to development of approaches to AV management that limit or avoid antibiotic use due to the emergence of antibiotic resistance, which has widespread implications.[19,20]

In this article, the authors conceptualize beyond just the correlation of how individual medications modify pathways of AV lesion formation. Instead, a broader view of the individual affected by AV is taken, with consideration of other underlying factors that are believed to contribute to a systemic imbalance or dysregulation, all of which provide their contribution to the development of AV. Figure 1 conceptualizes 6 patient-centric factors noted to play a role in a systemic imbalance, and depicts their suggested connection to the underlying inflammation seen in AV.

The Skin Response to Psychological Stress

AV flares are often reported in association with increased stress.[21-23] Stress is a *triple-edged sword* in people with AV. It can contribute to the development of AV flares, it increases after a flare of AV, and/or "hangs overhead like a dark cloud" as many

FIGURE 1. Conceptualization of underlying patient-centric factors contributing to the development of acne vulgaris. An increase in stress severity is connected to a cutaneous inflammatory response through the release of cortisol and Substance P.[27] Hormonal fluctuations driven by androgens stimulate sebum production and pro-inflammatory cytokines.[67] Diet and metabolism of macronutrients, vitamins, and minerals affect cutaneous health.[37] Dysbiosis of the microbiome in the skin and/or gastrointestinal tract drives a systemic inflammatory response.[17] Oxidative stress from external sources (UVA, UVB) or internal sources (lipid peroxidation) leads to cellular damage from ROS.[78] Lastly, immune activation in response to these factors drives a systemic inflammatory response, leading to the development or exacerbation of acne.[60]



Abbreviations: UVA, ultraviolet A; UVB, ultraviolet B; ROS, reactive oxygen species

individuals are stressed with the anxiety of wondering when the next AV flare will occur, since most are not predictable.[22,23] A recent cross-sectional study analyzed AV severity in female medical students and found that an increase in stress severity was strongly correlated with increased AV severity.[24] In another study, job stress was associated with increased severity of AV in women.[25,26] These results truly resonate, especially as many adult women are noted to have AV that recurs or persists beyond adolescence or develop new-onset AV usually during or after their mid-twenties. Higher stress levels and having a psychologically stressful job also correlated with localized, mandibular AV in women.[25] On a physiological level, it has been reported that the skin actively responds to stress through neurotransmitters, cellular immune responses, and hormonal fluctuations.[21] The generalized stress response generated by the hypothalamic-pituitary-adrenal axis (HPA axis) releases corticotropin-releasing hormone (CRH), which is responsible for the release of androgenic and glucocorticoid hormones such as dehydroepiandrosterone sulfate (DHEA-S) and cortisol respectively, both known to play contributory roles in the development of AV lesions.[27,28] Interestingly, AV lesions from female patients were found to have significantly higher levels of CRH in the sebaceous glands compared to healthy control skin.[29]

Specifically, within the PSU, systemic stress induces a localized, cellular inflammatory response directly within the skin. Keratinocytes express receptors for pro-inflammatory neurotransmitters (ie, nerve growth factor, histamine), making them an important link for neuro-endocrine interaction at the PSU level.[30] Moreover, keratinocytes, immune cells, and mast cells are all capable of synthesizing CRH,[31] which mediates lipid synthesis within sebocytes, thus modulating the PSU lipid composition.[31] Substance P (SP), a key neuro-inflammatory mediator released during local stress and noxious stimuli, accumulates around sebaceous glands.[32] In this location, SP may induce mast cell degranulation, which can augment the perilesional inflammatory processes by increasing the expression of the pro-inflammatory mediators interleukin (IL)-1, IL-6, and tumor necrosis factor-α (TNF-α).[32] SP has also been shown to act directly on the PSU by promoting proliferation and differentiation of the sebaceous gland and upregulating lipid synthesis by sebocytes.[32]

On a broader scale, daily stress can prolong wound healing time, believed to be an integral contributor to the resolution of AV flares, likely due to cortisol release, which can inhibit early inflammatory responses.[33] In a study of caregivers, a responsibility known to be psychologically stressful, wounds remained larger and took longer to heal compared to non-stressed controls.[34] The proinflammatory cytokine IL-1β response was impaired in the stressed caregiver group during exposure to lipopolysaccharides.[34] The involvement of IL-1β was later confirmed by studying the wound healing response in dental school students undergoing the acute stress of school exams compared to summer break.[35] IL-1β plays an important role in fibroblast chemotaxis and production of collagen, as well as immune response to foreign bodies, indicating that psycho-emotional stress can disrupt a healthy immune response, which is critical for normal wound healing.[33]

A systems-wide approach to understanding the multiple contributory factors that can drive AV development also allows us to consider the role of stress on other inflammatory cascades that impact AV. For example, chronic stress has been linked to oxidative stress in the skin, possibly through the renin-angiotensin system.[36] Angiotensin II stimulates NADPH oxidase-dependent reactive oxygen species (ROS) production in neutrophils, which also triggers the release of inflammatory mediators at the PSU, compounding the impact that stress may have in the development of AV.[36] The role of oxidative stress in the development of AV is discussed further in this review.

Diet and Metabolism

Dermatologists have long suspected a correlation between diet and AV development and/or flares, especially with excessive carbohydrate intake, high sugar-containing foods, and high dairy (milk) intake. There is now a more convincing body of evidence supporting the association between diet and AV.[15,37,38] It has been shown that a modern Western diet high in processed sugars and simple carbohydrates and low in fiber has increased the incidence of diabetes and unbalanced insulin levels, which correlates with AV severity.[38,39] A 2015 study showed that fasting insulin levels are higher in patients with severe AV than in a healthy control group.[39] Another study showed that participants who consumed a diet of low glycemic load substituted with high protein had a marked decrease in the total AV lesion counts compared to a group consuming a traditional high glycemic load diet.[38]

The modern hypothesis explaining the correlation between sugar intake and AV focuses on the glycemic load, blood glucose, insulin, and the association between insulin-like growth factors (IGFs) and cutaneous endocrine responses.[25-27] Receptors for insulin, the peptide hormone that regulates carbohydrate metabolism, and insulin-like growth factor-1 (IGF-1), an important trophic hormone that promotes bone and tissue growth, are both expressed in epidermal keratinocytes.[40] In fact, IGF-1 in patients with AV is significantly elevated compared to controls.[41] IGF-1 indirectly stimulates the nutrient sensitive kinase mammalian target of rapamycin (mTOR), which is a key regulator of cellular proliferation and lipid synthesis.[15] When activated, there is an increase in sebocyte growth and sebaceous lipogenesis, as well as increases in androgen hormone secretion.[15,42] High insulin levels also lead to altered proliferation of keratinocytes in the PSU.[15] Indirectly, low glycemic index foods also reduce free

androgens, mitigating the effects of hormonal dysregulation involvement in AV.

Besides carbohydrates and simple sugar consumption, some key vitamins and minerals may have contributory effects on the clinical manifestations and severity of AV. Zinc is a key cofactor in the regulation of protein and lipid metabolism and, specific to AV, it has been shown to be bacteriostatic against *C. acnes*, as well as reduce the pro-inflammatory cytokine TNF-α.[43] Deficiency in selenium has also been reported in AV patients.[44] Additionally, selenium supplementation has been shown to play a role in hormone regulation by decreasing the levels of the testosterone precursor dehydroepiandrosterone (DHEA) in female patients with polycystic ovary syndrome (PCOS), an endocrine disorder associated with AV as an established manifestation of androgen excess.[45] Additionally, low levels of vitamin D have been correlated with AV severity, predominantly visibly inflammatory AV lesions.[46] Supplementing with vitamin D in these patients has been noted to exhibit some improvement in the number of inflammatory AV lesions.[47] Finally, low levels of folate have been observed in AV patients.[48] Folate has many roles, but one of the most potential links to AV is its inhibitory effects on homocysteine (HCY) levels, which have been documented to be markedly elevated in patients with moderate-to-severe AV.[49] HCY degrades structural components of skin, stimulating the production and enzymatic activity of matrix metalloproteases (MMPs); some MMPs function to degrade elastin and collagen and can modulate AV lesion resolution and scarring potential.[50,51] Folate also has been hypothesized to play a role in the evolutionary adaptation to ultraviolet (UV) radiation to provide important repair mechanisms to photodamage.[52] Although the role of vitamins and minerals in AV warrants additional study, the rationale for proper supplementation based on the collective data reviewed above is well founded and can also provide other positive health benefits beyond just the skin.

The intake of essential vitamins and minerals is vital for good health, including for skin. For example, vitamin A is essential for immune activity, epithelial barrier function, and cell differentiation, but is not synthesized by the human body, so it must be consumed in amounts that are needed physiologically.[53] The correlation of oral vitamin A and its therapeutic effects for AV was first shown in a clinical study in 1942.[54] This eventually became the basis for the development of tretinoin in the 1960s and isotretinoin in the 1970s.[5,54] It has also been observed that low levels of vitamin C are associated with poor wound healing and compensatory thickening of the stratum corneum.[53] Taken together, these data suggest that appropriate levels of these and other vitamins and minerals could contribute to improving AV by supporting several of the important physiological mechanisms needed for healthy skin, with some observations more closely related to AV pathophysiology.

Skin and Gut Microbiome

Treatment of AV with systemic antibiotics has been well-established to be effective over several decades of experience and data, suggesting a bacterial component in the pathophysiology of AV.[55,56] It remains apparent that colonization with pro-inflammatory strains of *C. acnes* is a direct contributor to AV pathophysiology and reduction in these strains correlates with improvement in AV.[57] However, we recognize that *C. acnes* does not exist in a vacuum in the skin, and that there is a relationship of microorganisms within the skin microbiome, and even within the gastrointestinal (GI) tract, that can affect AV pathophysiology.[16,58] Differences in host response to strains of *C. acnes* and other microbiome changes that occur in AV may also affect AV severity.[12]

The top 4 major phyla on the skin are the same for both AV and healthy patients, with differences in diversity of some major microbes shown to correlate with individuals presenting with or without AV.[16,58,59] Moreover, the common use of topical and systemic antibiotics contributes to changes in diversity in the gut and skin microflora, allowing resistant bacterial strains to persist often over several months to years after discontinuation of antibiotic therapy.[58] The overpopulation of pro-inflammatory strains of *C. acnes* on the skin triggers several immune responses. These include stimulation of the release of inflammatory mediators (IL-17A and IFN-γ, IL-1α, IL-8, and TNF-α) through Toll-like receptors (TLR) on T lymphocytes; secretion of proteases, lipases, and hyaluronidases leading to tissue damage; accumulation of sebum due to lipogenesis by sebocytes; induction of antibacterial resistance to agents and host inflammatory cells; and contribution to AV scar formation through the release and modulation of MMPs.[12,58,60]

More recently, dysbiosis of the gut microbiome has been associated with many chronic inflammatory conditions, including AV, with 54% of AV patients reported to have marked changes showing dysbiosis in the GI tract microflora; these include a decrease in some organisms known to exhibit positive probiotic effects.[16,61,62] With >70% of the immune system reportedly found within the GI tract, the gut is an important location for many inflammatory and potentially pathophysiologic triggers.[63,64] Many factors contribute to changes in the gut microbiome, such as host physiology and genetics, antibiotic use, stress, diet, and underlying disease states.[65] Participants consuming a Western diet have been shown to often exhibit altered levels of gut microbes, highlighting the potential upstream implications of diet and metabolism on overall health, including AV development.[61,66] AV patients have been reported to have a decrease in gut microbial diversity and a loss of commensals such as *Faecalibacterium* and *Clostridiales*.[61] Dysbiosis of the gut microbiome has been linked to diminished intestinal barrier integrity (increased intestinal permeability) and increased

lipopolysaccharide endotoxins in circulation, potentially triggering a generalized inflammatory response through TLR-4 and CD14.[66] Overall, research to date supports a link between microbiome alterations, systemic inflammation, and overall health. We are in the early stages of understanding and defining details related to the microbiome, both overall and within specific body systems such as skin. Thus far, there is good evidence to show that the status of the microbiome plays an important role in maintaining overall health homeostasis and can contribute to the pathophysiology of specific disease states including AV.

Hormones

The role of the endocrine system, especially androgens, is well-established as a mandatory component in the development of AV.[67] In the 1930s, the correlation between a woman's menstrual period and AV led doctors to label AV as "chastity pustules," for which they prescribed laxatives to help rid the body of the build-up of toxins.[68] Over almost a century, our understanding of the skin and AV has come a long way, and we now know that hormones, primarily androgens, drive AV in both men and women. It is also now recognized that the skin itself is an endocrine organ, capable of synthesizing androgens, such as dihydrotestosterone, within itself.[67,69,70] A systematic review of over 1,000 studies found that testosterone and progesterone may be elevated in AV patients, but that estrogen is significantly lower in AV patients.[71] Specifically, excess circulating androgens can be associated in some patients with AV, but many exhibit normal androgen levels on blood testing, supporting the important role of local androgen production in AV-affected skin.[41,71] It has been shown that patients with AV produce higher levels of testosterone and 5α-dihydrotestosterone (DHT) in their skin than healthy individuals.[41] It is also established that the sebocytes possess all the necessary enzymes for both synthesizing androgens and for converting testosterone to DHT, making the local skin environment the primary site for androgen activity in AV in most affected patients.[71,72] DHT exerts its effects via the nuclear androgen receptor. It has been shown to directly stimulate TNF-α and IL-6, indicating a strong correlation between androgen activity in the skin and pro-inflammatory cytokine production in AV.[73,74] The hormone DHEA also regulates sebum production and has been indicated as an important target in postmenopausal women.[72] It also has been shown to be correlated with IGF-1 levels, which are higher in men and women with AV.[72] As noted above, PCOS, an endocrine disorder induced by hyperandrogenism, is characterized clinically by the presence of AV as one of the visible manifestations of androgen excess.[75]

Oxidative Stress

The skin, and particularly the face, is regularly exposed to exogenous pollutants and irritants as well as UV radiation and ozone, leading to an accumulation of reactive oxygen species (ROS).[76] These ROS, which are highly reactive and unstable chemical entities, have been shown to accelerate adverse skin changes including the appearance of aging and pigmentation, roughness, and wrinkles.[76]

Clinical evidence also indicates that oxidative stress may play a role in AV.[77] Biomarkers for lipid peroxidation, such as blood serum levels of malondialdehyde (MDA), are significantly higher in patients with AV than in their controls.[78] Enzymes with antioxidant capacity such as catalase, superoxide dismutase, and total antioxidant capacity are also significantly lower in patients with AV compared to controls, likely reflecting their consumption, at least partially, by interacting with ROS exposure with inadequate reserve.[78] Accumulation of lipid peroxide (LPO) and sebum oxidation are also higher in comedones of patients with AV than from the facial stratum corneum.[79] In addition to LPO, the inflammatory mediators IL-1α and NF-κB were also found to be higher in comedones, indicating a potential link between oxidative stress, inflammation, and AV lesion formation.[79]

On a mechanistic level, both intrinsic and extrinsic stressors can be a source of ROS generation: as a normal byproduct of mitochondrial metabolism; chronic psychological stress; environmental pro-oxidant factors including UVA, UVB, visible light, and infrared light exposure; and ozone exposure.[76,80] ROS due to these stressors include superoxide radicals, hydrogen peroxide (H2O2), hydroxyls, singlet oxygens, peroxyl radicals, and nitric oxide (reactive nitric species).[81] Our intrinsic antioxidant defense system is responsible for scavenging ROS and neutralizing them.[81,82] This system includes enzymatic antioxidants, such as superoxide dismutase and catalase; non-enzymatic antioxidants such as glutathione, and vitamins C and E; and transcriptional activation of inflammatory responses in the follicular epithelium.[80,83]

Over time, and with overwhelming exposure to ROS sources, accumulation of ROS leads to oxidative damage to cellular components such as proteins, lipids, nucleic acids, and the cell membrane.[80] Lipid peroxidation of the cell membrane, if subtoxic, may trigger repair mechanisms through antioxidant defense or signaling pathways that are adaptive.[80] Otherwise, when the oxidative stress overwhelms the capacity of the cell to repair, it will trigger cellular damage, with functional impairment and sometimes necrosis, contributing directly to skin senescence.[80] There are a few ROS-generating pathways specifically implicated in AV. Accumulation of neutrophils at the site of comedones leads to an increase in the generation of ROS.[77] *C. acnes* has also been shown to induce neutrophil secretion of ROS.[77]

Lipid peroxidation, the oxidative degradation of lipids, is an important mechanism involved in the pathophysiology and progression of AV.[80] Indeed, lipid peroxides, the chemical product, are higher in comedones of patients with AV and have been shown to affect keratinocyte proliferation and

stimulate pro-inflammatory cytokine release.[79,80] They also bind to the peroxisome proliferator activated receptor-gamma (PPAR-γ), triggering the production of lipids from sebocytes.[84] Activation of PPAR-γ has also been shown to be involved in androgen-mediated signaling and regulation of glucose and lipid metabolism, once again suggesting cross-talk between many potential pathophysiologic cascades in the development of AV.[74] Interestingly, these links on cursory review appear to be unrelated and involve distinctly different body systems and functions, however, cross-talk that can affect pathophysiology has been identified.

Immune Function

Immunologic responses, both local and systemic, have become progressively recognized as important in AV pathophysiology. Studies suggest that *C. acnes* can trigger immune responses in AV through multiple, direct pathways.[12,60] A primary immune response occurs through interaction with specific TLRs, which are innate pattern recognition receptors, expressed on numerous cell types present within the skin, such as keratinocytes, sebocytes, dendritic cells, lymphocytes, mast cells, and resident macrophages.[60] The innate immune system also responds to *C. acnes* proliferation and cellular interactions through inflammasomes — receptors that induce inflammation in response to microbes, and by stimulating antimicrobial peptide (AMP) activity, small molecules that have a wide range of inhibitor effects against bacteria, fungi, parasites, and viruses, but can respond in disease states such as AV that involve a pathogenic commensal organism.[60] Finally, *C. acnes* induces the production of MMPs, which are zinc-dependent protease enzymes that can degrade many structural components of the extracellular skin matrix, with involvement in modulation of AV-affected skin including potential scarring.[60,85]

Subclinical inflammation of the skin begins early in the development of AV.[12,74] Based on data evaluating the sequence of AV lesion formation, perilesional lymphocyte accumulation with the recruitment of inflammatory mediators is thought to precede or occur simultaneously with follicular hyperkeratinization (microcomedone formation) in the PSU. In vitro studies show that the application of pro-inflammatory cytokines such as IL-1 on PSU induces hyperkeratinization.[85] In addition, other pro-inflammatory cytokines such as TNF-α and interleukins such as IL-8 have been shown to be higher in AV lesions compared to uninvolved skin, suggesting that many cytokines and other mediators contribute collectively to the development of AV lesions.[86]

Beyond the direct involvement of the immune-inflammatory response at the PSU, other noxious stimuli indirectly trigger heightened immune responses. Oxidative stress causes direct and immunologic cellular damage.[77] Microbiome dysbiosis can activate the innate immune system to defend from proliferation of pathogenic microbial organisms.[65] High glycemic index diets and insulin fluctuations can induce a generalized inflammatory response, and stress can promote a heightened immune response on both local and systemic levels.[36,42] DHT upregulates sebaceous lipid formation and pro-inflammatory cytokine production (ie, TNF-α, IL-6) by sebocytes on the PSU, supporting a link between hormonal interactions and an immune-inflammatory response.[71] Once activated, many inflammatory mediators such as TNF-α, IL-6, SP, and TGF-β, are expressed, generating "a pro-inflammatory soup" at the PSU.[27] With this, neutrophils are recruited to the site of inflammation, further damaging the sebaceous gland and follicular epithelium.[27] This follicular wall damage causes porosity within the wall structure, resulting in leakage of follicular contents into the surrounding dermis which induces both direct and indirect inflammation, even in the absence of obvious follicular wall rupture.[12]

CONCLUSION

The underlying causes of AV have conventionally focused on the major individual pillars of pathophysiology and how individual medications can mitigate these pathways to improve AV. In this article, this prior approach is not discarded. Rather, there is a strong suggestion, with good underlying support, to integrate a more comprehensive management approach to include other underlying systemic factors, many of which are likely to relate directly to AV. In this review, we have identified the 6 major underlying patient-centric factors: psycho-emotional stress, diet and metabolism, hormonal fluctuations, microbiome dysbiosis of the skin and gut, oxidative stress, and immunologic responses. Each of these contributes to an overall generalized dysregulation that includes a variety of immunologic and inflammatory responses, with many believed to contribute to the development and/or exacerbation of AV. This broadened perspective on AV management allows for a more expanded therapeutic approach, beyond only the long-standing conventional method of matching medications with what visible AV lesions are present, coupled with good general skin care.

As a second part of this review, Burgess et al[87] will present supporting clinical evidence for various ingredients to address these 6 underlying patient-centric factors.

DISCLOSURES

Dr Del Rosso and Dr Harper are clinical investigators for Nutraceutical Wellness LLC but have not received compensation or services for any aspect of the submitted work. Dr Farris is a paid advisor for Nutrafol and Nutraceutical Wellness LLC. Dr Baldwin declares no conflict of interest. Dr Hazan and Dr Raymond are employees of Nutraceutical Wellness LLC.

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