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REVIEW

Unveiling the Nuances of Adult Female Acne: A Comprehensive Exploration of Epidemiology, Treatment Modalities, Dermocosmetics, and the Menopausal Influence

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Abstract: Previously considered a skin disease exclusively affecting adolescents, characterized by inflammatory and non-inflammatory skin lesions, acne vulgaris is now increasingly observed in adult life, including post-menopause. Today, adult female acne (AFA) is a common chronic inflammatory disease of the pilosebaceous unit, with polymorphic lesions presenting as open or closed comedones, papules, pustules, and even nodules or cysts, often with the presence of sequelae. AFA may persist from adolescence or manifest de novo in adulthood. Its etiology is multifactorial, involving genetic, hormonal, dietary, and environmental factors, yet still incompletely understood. Increased sebum production, keratinocyte hyper-proliferation, inflammation, and reduced diversity of *Cutibacterium acnes* strains are the underlying disease mechanisms. During menopausal transition, a relative increase in androgen levels occurs, just as estrogens begin to decline, which can manifest itself as acne. Whereas most AFA exhibit few acne lesions with normo-androgenic serum levels, baseline investigations including androgen testing panel enable associated comorbidities to be eliminated, such as polycystic ovarian syndrome, congenital adrenal hyperplasia, or tumors. Another interesting feature is AFA's impact on quality of life, which is greater than in adolescents, being similar to other chronic diseases like asthma. The therapeutic approach to AFA depends on its severity and associated features. This review investigates the intricate facets of AFA, with a specific focus on incidence rates, treatment modalities, and the curious impact of menopause. Utilizing insights from contemporary literature and scientific discussions, this article seeks to advance our understanding of AFA, offering new perspectives to shape clinical practices and improve patient outcomes.

Keywords: adult female acne, epidemiology, treatment, dermocosmetics, menopause, hormonal dynamics

Introduction

Among teenagers, acne vulgaris is a common inflammatory disorder of pilosebaceous units, affecting more than 95% of boys and 85% of girls.[1–3] Over recent years, a significant increase in a specific acne subtype has occurred, affecting women over 25 years of age defined as adult female acne (AFA).[4] Not only women of childbearing age are affected, but also those who are postmenopausal (PMA) and those suffering from endocrinological disorders.[5] The perception of acne as a transient affliction that primarily affects adolescents has been evolving, leading to a new awareness that this skin condition could persist into adulthood or even occur de novo in adult women. These two forms of acne are called persistent acne and late-onset acne.[4] For several experts, there is a third form of acne in relation with the timing of lesion onset. In this latter scenario, acne starts during adolescence, followed by disappearance of all target lesions, yet with

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lesions returning in a particular topographical distribution during adult life. This type of acne is referred to as recurrent acne.[6] As the trend of global population ageing continues, people's healthcare needs essentially change, creating new unmet needs to be addressed.

Although AFA's etiopathogenesis is incompletely understood, it is a multifactorial inflammatory disorder of the pilosebaceous unit.[7] The condition is immune-mediated and androgen-triggered. Other factors, such as stress, sleep disorders, skin manipulation, excessive washing, smoking, cosmetics, as well as using drugs like anabolic steroids and some progestins probably play a role.[2] Furthermore, the deficiency of the epidermal barrier function, resulting in a subsequent increase in trans-epidermal water loss, has been incriminated to be a key player in acne onset.[8] Resistance mechanisms of *Cutibacterium acnes* (*C. acnes*), such as biofilm formation, are also deemed potential contributors to the chronic nature of the condition in adulthood.[9]

In pathophysiological terms, the following four interconnecting factors clearly contribute to the development of acne: 1) excess sebum production under androgen control leading to sebaceous gland hyperplasia; 2) altered follicular hyperkeratinization resulting in blockage of serum secretion; 3) sebaceous gland colonization with *C. acnes*, previously named *Propionibacterium acne* (*P. acnes*), which is also involved in the qualitative sebum alteration, rendering it pro-inflammatory; 4) chronic inflammation under the control of complex innate and acquired immunological mechanisms.[10,11] In menopausal women, hormones, and particularly androgens, play a vital role. During the menopause, estrogen levels tend to fall sharply, while the ovaries continue to secrete androgens. This causes a disparity between estrogen and androgen levels, with a relative androgen excess.[12] The subsequent hormonal imbalance stimulates sebaceous gland growth and sebum production. Nevertheless, unlike postmenopausal women, most patients suffering from AFA exhibit normal androgen levels.[13] Yet, in these patients, sebaceous glands can display an increased sensitivity to or intracrine overproduction of androgens, resulting in hyperactivity and amplified serum production.

Most prior studies focused on acne have highlighted acne impacting negatively on patient quality of life (QoL), possibly including signs and symptoms of depression and anxiety, such as anger and low self-esteem.[14–17] Although AFA is mainly of mild intensity, its ensuing impact does not necessarily correlate with the severity of acne lesions. Patients with mild-intensity disease may find this condition exerts a high impact on their QoL. It must also be stressed that the impact of acne on patients' QoL was revealed superior in adults versus adolescents, as well as in women versus men. Hence, a 2023 published study revealed that atrophic acne scarring had a significant psychological impact on patients' QoL in the form of embarrassment and self-consciousness.[18] In a 2022 paper, facial and truncal acne turned out to be associated with a greater adverse impact on patients' QoL in comparison with facial acne alone, irrespective of the severity degree of facial acne.[19] Another publication highlighted that after age 20, acne accounted for an almost 2.5-fold higher proportion of dermatology visits among women versus men.[20] It is thus crucial that these patient needs must be properly addressed, with patients referred to dermatologists and general practitioners as necessary, given that acne is a chronic disease significantly impacting the different stages of life.

Concerning AFA management, multiple options are available, including different topical medications.[21–24] Nevertheless, no topical medication is able to address on its own all the causal features involved in the development of acne. Therefore, systemic drugs must be added to topical agents in moderate to severe acne cases.[25] Treatment of acne should be initiated as early as possible to lessen the risk of scarring and its negative psychological impact.[7] Management must always be tailored to the individual patient's need, taking account of the acne's type and severity, as well as the patient's preferences, her ability to apply treatment and adhere to the prescribed regimen, in addition to her psychological status. The role of dermocosmetics, meaning skin care solutions that contain sophisticated active ingredients to care for symptoms of dermatological conditions like acne, is outlined as well in this review paper.

Several factors proven to trigger AFA are likewise involved in PMA, including cosmetics, dietary factors, obesity, smoking, drugs, sleep deprivation, and stress.[7] Women with PMA often exhibit increased skin sensitivity, with a higher frequency of post-inflammatory erythema (redness), hyper- or hypo-pigmentation, and scarring. These cosmetically disfiguring alterations may lead to depression and negatively impact on QoL.[26]

Methodology

The Google Scholar and PubMed databases were searched for articles written in English focused on acne, with the following key words applied: adult female acne, post-menopausal acne, post-adolescent female acne, etiopathogenesis of female acne, and prevalence of adult acne. All articles that discussed the features of AFA, dating up to June 2023, were selected. More than 60 publications were thus compiled, consisting of prospective, retrospective, and review articles.

Based on the compiled literature, this review article primarily sought to investigate the intricate facets of AFA, with a specific focus on frequency rates, treatment modalities, and the curious impact of menopause. Utilizing insights from contemporary literature and scientific discussions, this article primarily sought to advance our understanding of AFA and PMA characteristics, while providing valuable perspectives to inform clinical practices and policies, thereby improving patient outcomes.

Epidemiology of Adult Female Acne

Prevalence

In spite of AFA being increasingly seen in dermatology clinics, the frequency rates of AFA are still insufficiently studied. Our compiled literature clearly documented that acne vulgaris occurs in people of all ethnicities and races, yet to different degrees. Although disease pathology and treatment modalities are likely similar across all skin phototypes, darker-skinned patients tend to display higher incidence rates of acne sequelae, including post-inflammatory hyperpigmentation and keloidal scarring.[27] This article's authors concluded their research emphasizing that, when selecting therapies for patients of color, clinicians ought to seek a balance between aggressive early therapy, primarily directed against inflammatory acne lesions, and more gentle subsequent treatments, chiefly designed to avoid skin irritation.[27]

Scientific literature from the United States of America (USA) revealed that of all adult acne cases, women were affected more commonly than men, given that approximately 12 to 22% of women suffered from adult acne versus only three percent of men.[28] Another differentiating aspect noticed between adolescent acne and AFA is the latter's more intense impact on quality of life (QoL).[29] A survey conducted in France involving 3394 women disclosed a total acne prevalence of 41% among adult women.[30] Moreover, 41% of adult acne patients had not experienced acne during their adolescence, thus representing late-onset acne cases. Premenstrual flare and stress were revealed associated with worsening acne in 78% and 50% of patients, respectively.[30] Among USA survey involving 208 AFA patients, 51.4% were White/Caucasian, 24.5% Black/African American, 11.1% Hispanic/Latino, 7.7% Asian, and 5.3% other. These data clearly demonstrate that AFA actually occurs across the most common ethnicities.[31] Nevertheless, acne therapy can be particularly challenging in darkly pigmented skins. The acne lesions themselves and the aggressive products often applied to treat acne flare-ups commonly provoke post-inflammatory hyperpigmentation.[32] Using gentle cleansers in addition to products designed to control inflammation and bacteria are likely to contribute to faster, more consistent results.[32]

A 2021 cross-sectional descriptive study of 56 adult women aged 25 years and over was carried out in Lagos, Nigeria.[33] AFA was observed in 19.3% of female patients seen in the clinic. Among these, acne was considered persistent in 55.4% and late-onset in 44.6% of cases. Acne scars were observed in 87.5% and post-inflammatory hyperpigmentation in 65.3%.[33]

A large-scale international study conducted across various European countries including 323 outpatients and 31 hospitalized adult patients, 61% of whom were female, reported that the face was the most commonly affected body part.[34] Predominant eruptions were pustules and papules. Overall, 38.7% of patients displayed a concomitant systemic chronic disease, 15.2% an endocrinological disorder, and 6.2% thyroid gland dysfunction. This analysis led the authors to conclude that in AFA patients, endocrinological investigations are likely warranted to exclude a systemic disorder, especially when acne is not the only manifestation of hyperandrogenism.[34] This appears to be particularly true in women suffering from late-onset acne. Here, it must be noted that, in most studies focused on AFA, heterogeneous inclusion criteria were applied, with acne being either isolated or associated with other androgenic abnormalities. Therefore, it is not entirely clear whether the high acne presence in the studied patient groups was indeed due to a real increase in acne rates or possibly accounted for by increased published information on the disease and its treatment. Truly, growing online media coverage could possibly lead to an increased number of women seeking specialized medical care.

A large-sale prospective study was carried out in Latin America and the Iberian Peninsula, involving 1384 patients, aged between 25 and 60 years old, originating from 21 different countries.[35] This international study sought to better identify the disease characteristics, in addition to biological, social, and environmental risk factors contributing to disease severity. The authors concluded their research stating that the characteristics of adult acne may somewhat differ from those of adolescent acne, yet have largely similar disease presentations.

Genetic factors are clearly involved.[30,36] To illustrate, if the mother developed acne during adulthood, the child is more likely to suffer from acne during this period of time, as well.[30] While adolescent acne is primarily due to the new influx of hormones during puberty, hormonal fluctuations during adulthood, as observed during pregnancy and menstruation, can likewise trigger the occurrence of acne flare-ups. During the peri-menopausal phase, these women may instead experience an aggravation of their acne, accounted for by the imbalance between estrogen and androgen levels.[12] While teenagers often develop acne around their cheeks and forehead, several authors described acne mostly occurring on the chin and around the mouth in AFA/PMA women.[37] Moreover, female acne often causes greater distress in adults versus adolescents. The disease impact may thus be more pronounced in AFA, resulting in higher psychosocial anguish and discomfort.[37] In addition, treatment modalities for AFA and acne in pre- and post-menopause significantly differ, given that oral contraceptives must be prescribed with caution or are even contra-indicated for post-menopausal women.

In summary, numerous questions still remain unanswered regarding AFA frequency rates. What are the main etiological factors related to acne in adult women by region, country, or continent? Has this percentage remained active since puberty or adolescence? How long is the active disease likely to last in these women? And, for how long do the women affected usually need to receive anti-acne treatment? Additional research is thus required to further alleviate symptoms and improve patient outcomes.

Contributing Factors

As a multifactorial disease, acne vulgaris involves the overproduction of sebum, irregular shedding of cutaneous cells, diminished diversity in *C. acnes* strains within the pilosebaceous unit, and particularly inflammation.[38,39] Acne is an inflammatory, immune-mediated, and androgen-triggered condition, with inflammation likely playing a predominant role. Using histopathological examinations, inflammation could indeed be detected not only in inflammatory lesions like pustules and papules, but even around non-inflammatory acne lesions like comedones and in perilesional areas.[38,39]

Androgens

The role of androgens in acne vulgaris is well established. Testosterone with its metabolites, dehydroepiandrosterone sulfate (SDHEA) and dihydrotestosterone (DHT), has been shown to stimulate both the growth of sebaceous glands and their production of sebum.[7,26] These hormones also enhance hyperkeratinization leading to the formation of microcomedones.[40,41] In parallel, the innate immune responses are activated through contact with *C. acnes*, possibly even prior to the follicular hyperkeratinization process.[8] Indeed, on skin biopsy slides, infiltrates of lymphocytic memory and effector T-cells were observed at the very beginning of acne lesion developement.[8,42] Furthermore, *C. acnes* has been proven connected to sebocytes, keratinocytes, and dendritic cells, by Toll-like receptors 2 and 4, thereby triggering the activation of monocytes, which are essential cells of the innate immune system. Upon activation, these monocytes release two major interleukins (ILs), IL-8 and IL-12. Of note, IL-12 is known to be the major inflammatory cytokine in charge of immune response processes directed against the invading gram-positive bacterium, *C. acnes*.[43] IL-8, on the other hand, plays a key role in recruiting neutrophiles that subsequently release several lysosomal enzymes, which then destroy the follicular epithelium, so as to aggravate the inflammatory response. Inflammation is increasingly recognized as the starting point of the acne process. In a 2021 paper, the involvement of activated mast cells was reported to play a crucial role.[42] In the very early stages of acne, these activated mast cells are the main producers of IL-17 and the IL-17-induced inflammatory responses at the origin of an altered skin microbiome homeostasis, also called dysbiosis, notably involving *C. acnes*.[42]

Numerous scientific papers have further stressed the etiological role played by androgens. A review paper by Zouboulis et al compiled several clinical observations supporting the positive link between serum androgen levels and acne lesion counts.[44,45] These authors highlighted the near-absence of acne lesions in men with androgen insensitivity syndrome or early castration.[44] Moreover, the development of acne in small children with excessive androgen levels, also

called hyperandrogenism, was shown associated with either virilizing ovarian tumors or congenital adrenal hyperplasia.[44] It must, however, be stressed that only a small percentage of AFA patients display clinical evidence of increased androgen levels. Instead, the majority of them exhibit increased androgen receptor sensitivity, meaning that their receptors excessively react to androgen stimulation, with increased production of hormones by sebocytes.[46,47] Should this be the case, the presence of other clinical modifications associated with acne must urgently be searched for, such as hirsutism, change of voice, or menstrual cycle irregularities. Polycystic ovary syndrome (PCOS) may also be an underlying cause of acne.[48] Another factor to take account of is that, with age, many patients tend to increasingly use medication. In some countries, like Brazil, the use of anabolic steroids by adult women, seeking to improve body definition, is quite common nowadays.[49]

In vitro experiments have revealed that androgens like testosterone do not alter sebum production completely on their own. These hormones most likely require in vivo co-factors like peroxisome proliferator-activated receptor (PPAR) ligands, enabling them to mediate their effects at the sebaceous gland level.[50] These PPAR ligands likely play a crucial role in inflammatory acne characterized by redness and painful pimples.[51]

PCOS, a very common endocrine disorder afflicting reproductive-aged women, is the main acne-associated type of endocrinopathy.[52,53] Typically, the syndrome's triad encompasses hyperandrogenism, chronic anovulation, and polycystic ovaries. Accordingly, PCOS women often experience dermatological manifestations of hyperandrogenism, including hirsutism, acne vulgaris, and androgenic alopecia. The main diagnostic findings comprise hyperandrogenism, chronic anovulation, and polycystic ovarian morphology, as documented on ultrasound (US). In severe cases, virilization signs may be apparent. Treatments are likely to improve the clinical manifestations of excess androgen production, normalize menses, and ameliorate metabolic syndrome and cardiovascular complications, including excess weight and blood lipid parameters. Early diagnosis and consequent treatment can prevent metabolic complications and emotional distress negatively impacting on the patient QoL.[26]

Medications

Acne in adult women may either be generated or aggravated by drugs. Various drugs may provoke acne, referred to as drug-induced acne (DIA). This form of acne is characterized by a medical history of drug intake, abrupt onset, and an unusual age of onset, with a sudden eruption of inflammatory papules or pustules.[54] Most often, acne lesion location is beyond the seborrheic zone. Corticosteroids, anabolic steroids, vitamin B12, halogens, isoniazid, lithium, some progestins, and several new anticancer agents all undoubtedly harbor causal relationship with acne. A DIA diagnosis is established by detailed history with a record of drug onset, dosage regimen and therapy duration, absence of additional triggering factors, as well as a clinical relationship between drug intake and onset of acne-like eruptions.[54] In most cases, drug discontinuation is clearly followed by decrease in acne lesions.[54]

Acne can be generated by several internal and external body factors, including genetic disposition, hormone levels, diet, smoke, pollution, and stress.[1,55] Clearly, genes and environmental factors often interact, though the exact nature of this interaction is not fully understood. Modern life is, of course; filled with stress, including socioeconomic pressure, light stimuli, and noise. All this may be detrimental to both our physical and emotional health.[1] Also women are even more at risk than men of developing mental health problems, including anxiety and depression.[56,57] Sleep deprivation is an additional condition that negatively impacts on women's health, through its influence on hormonal secretion and the immune system.[1] Moreover, an association between exposure to ambient air pollution and acne occurrence has been observed within the adult patient population.[10]

The Western diet is characterized by a high intake of dairy products, as well as of foods with high glycemic index (GI) content. Several studies have demonstrated that this Western diet can affect the levels of hormones implicated in acne pathogenesis.[58] Of note, GI represents a 1 to 100 scoring system, commonly used to determine how quickly carbohydrates are digested, absorbed, and metabolized.[59] In various clinical trials, high-GI diets (>55) were linked to poorer blood glucose control, higher postprandial insulin levels, and elevated insulin-like growth factor 1 (IGF-1) levels.[60] All these factors are likely to influence acne's development and severity.[61,62] In contrast, low-GI diets were shown to decrease fasting IGF-1 levels. Accordingly, such diets may likewise alleviate acne problems.

The skin microbiome and its implication in acne have lately attracted the attention of numerous scientists. Hence, the paradigm shift that has occurred in our understanding of *C. acnes'* role in the development of acne.[63] Today, it is not *C. acnes* hyperproliferation that is deemed the acne-causing element, but rather the loss of balance between the different *C. acnes* phylotypes. The diversity loss of *C. acnes* phylotypes actually acts as a trigger for innate immune system activation, resulting in enhanced cutaneous inflammation. A predominance of *C. acnes* phylotype IA_1 has been observed, with a more virulent profile in acne than normal skin.[63,64] Given that commonly used topical and systemic antibiotics induce cutaneous dysbiosis,[65] our new understanding of acne's pathophysiology has prompted a change in direction with respect to acne treatment. Therefore, we might soon be able to develop highly-individualized acne therapies.[66,67] Such alternative treatments, involving microbiome modifications, most likely represent the next generation of "ecobiological" anti-inflammatory treatments.

Given this, it becomes understandable why, in 2008, Prof. Brigitte Dréno, a highly recognized expert in the field of acne research, alerted the medical and scientific community to a common misconception concerning acne management.[37] She vehemently stressed that AFA management should not consist of simple medical agents directed against acne symptoms. Instead, AFA management should encompass a holistic approach targeting the patient as a whole, with her individual lifestyle factors, preferences, and past medical history, as well as the acne's impact on her quality of life.[37]

Impact on Quality of Life

Several studies focused on AFA have clearly demonstrated that acne lesions negatively impact patient QoL, as evidenced by the presence of anxiety and depression signs, including low self-esteem and anger.[14–16] The impact of acne on patient QoL was not necessarily found to be correlated with the acne lesions' severity. Patients with mild-intensity disease may in fact experience a high negative impact on their QoL. It must also be stressed that the impact of acne on patient QoL was shown to be superior in female versus male patients, as well as in adults versus adolescents.[68] A report published in 2022 revealed facial and truncal acne to be associated with a greater adverse impact on patients' QoL compared to facial acne alone, irrespective of the severity of the facial acne.[19] Another publication reported that after age 20, acne accounted for an almost 2.5-fold higher proportion of dermatology visits among women versus men.[20] It is crucial that patients' needs be properly addressed. Consequently, patients must be referred to dermatologists and general practitioners as necessary. Acne is currently considered a chronic disease that has different impacts across the stages of life, and treatments must be initiated and subsequently adapted over long periods of time. It must also be stressed that even mild atrophic acne scars were associated with substantial emotional, social, and functional concerns in the affected patients.[19]

Issues Relating to Diagnosis

The diagnostic approach in patients with acne is primarily based on the clinical examination and associated findings. In the presence of hirsutism or female pattern hair loss, a full hormonal evaluation is warranted. Even in the absence of increased testosterone levels, the patient most likely displays increased hypersensitivity of androgen receptors or increased intracrine activity.[13,29]

In all cases, a thorough medical history is warranted, searching for information regarding drug intake and tobacco consumption. The subsequent physical examination should search for symptoms related to hyperandrogenisms, such as hirsutism, amenorrhea, or alopecia. In the presence of acanthosis nigricans, it is essential to rule out peripheral insulin resistance, which would require a full laboratory test assessment to be implemented.[69] In obese patients, evaluation for metabolic syndrome should be initiated.[70]

Acne is generally a clinically-made diagnosis, without requiring additional testing (Figures 1 and 2). Yet, in certain cases, a differential diagnosis with rosacea must be made. Rosacea mostly presents with inflammatory papules and pustules, on an erythematous background, along with telangiectasia. Unlike rosacea, the presence of comedones in acne patients is a supporting sign for establishing the correct diagnosis. The features of gram-positive, gram-negative or *Malassezia* folliculitis can also mimic acneiform eruptions, possibly leading to erroneous diagnosis and improper management.[71] Acneiform eruptions, mostly linked with the ingestion of certain drugs and chemicals, can confound the clinician and thus lead to an incorrect diagnosis of acne.

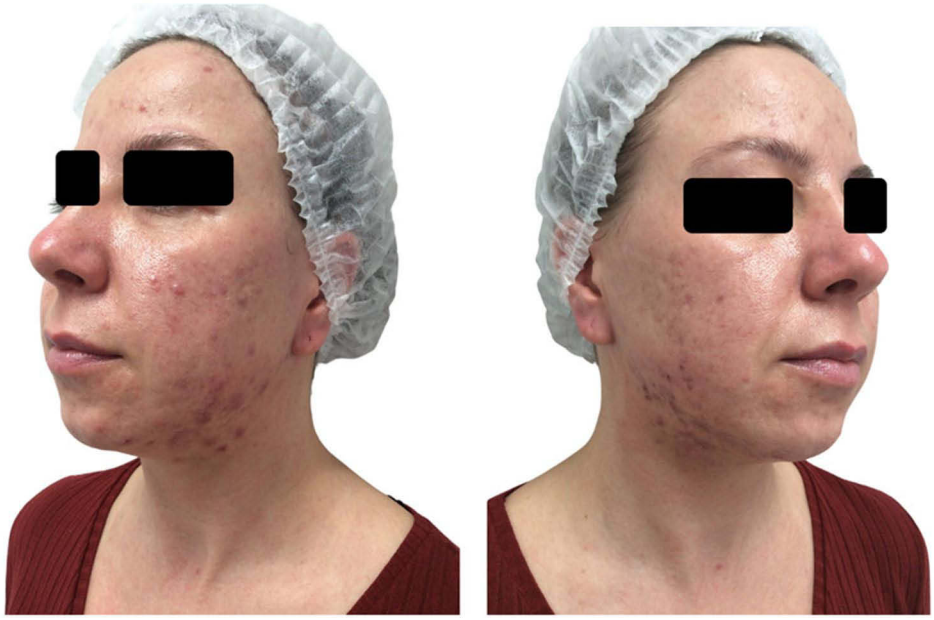

Figure 1 Clinical case of acne in an adult woman - 37-year-old normoandrogenic patient with moderate acne on the face and neck associated with dyschromia.

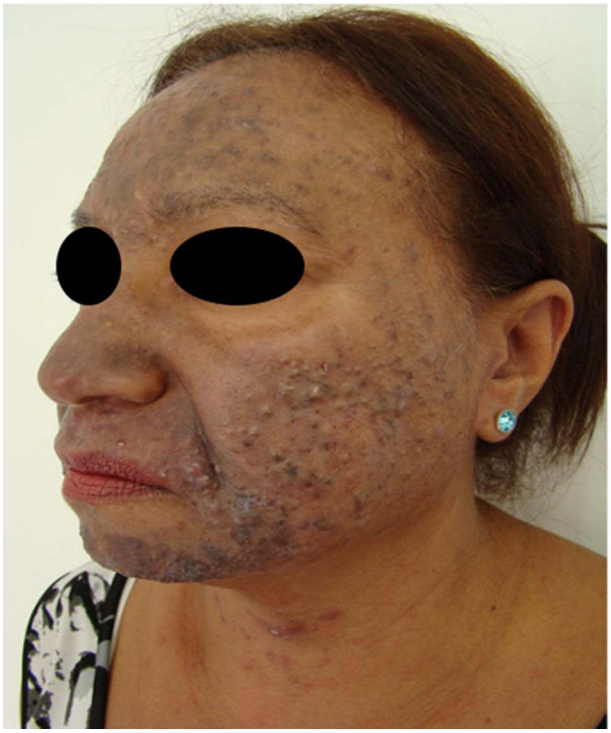

Figure 2 Clinical case of acne menopausal adult woman - 54-year-old normoandrogenic patient with moderate to severe acne on the face and neck associated with dyschromia.

Treatment Modalities

With a holistic health approach in mind, clinicians should at all times look at the patient as a whole, both mentally and physically, prior to initiating AFA therapy.[72] Accordingly, treatment must be targeted to each individual patient, with careful consideration of their distinctive features and circumstances. Such individual features should comprise the following: extent, severity, and duration of disease; response to previous treatments; predisposition to scarring and post-

inflammatory hyperpigmentation (PIH), in addition to patient preferences, mindset, and lifestyle, including sun tanning, smoking, nutrition, family planning, professional life and sporting activities. Likewise, skin sensitivity must be assessed.[73] These unique AFA features have led to the publication of recent guidelines with specific therapy recommendations for these patients.[7]

The following presents a brief overview of the dynamic treatment landscape, encompassing traditional therapies, emerging pharmaceuticals, and holistic approaches, all addressing the unique needs of AFA. Multiple options are available on the market, which are broadly similar to those designed for adolescent acne. In all patients, the choice of treatment depends on both the etiology and severity of acne lesions, along with the patient's response to prior treatments, patient's skin type, and associated features.

Topical Therapies

Topical therapies are recommended as first-line approach in mild AFA, as well as for maintenance treatment.[74] In mild-disease cases, topical retinoid or benzoyl peroxide, either as mono-therapy or in combination with topical antibiotics and azelaic acid, is primarily recommended. Of note is that topical agents are active only where and when they are applied. Accordingly, they must be applied onto all skin areas that are prone to acne. Moreover, no single agent has so far been proven able to target all the pathological aspects relating to acne. For the same reasons, the combination of different topical agents or addition of systemic drugs to topical therapy is often necessary.[21] In most cases, maintenance therapy is required to prevent acne recurrences.

Being bactericidal for *C. acnes*, benzoyl peroxide improves both inflammatory and non-inflammatory lesions.[22] Owing to its mechanism of action (oxygen introduction into follicles), resistance to benzoyl peroxide is rather uncommon. Nevertheless, unwanted effects like irritant dermatitis or cloth staining may occur.[75] This bactericide should be employed with caution in older women, as it can lead to skin dryness and irritation.[26] Topical antibiotics like clindamycin and erythromycin exhibit bacteriostatic activities against *C. acnes*, in addition to anti-inflammatory activity.[76] Nevertheless, these agents should not be prescribed as monotherapy, owing to their ability to induce bacterial resistance.[77]

Topical retinoids, including tretinoin and adapalene, have proven able to correct abnormalities pertaining to follicular keratinocytes, while being simultaneously active in treating inflammatory lesions, as well as in preventing the formation of comedones. Moreover, these agents block inflammation by reducing the expression of Toll-like receptors 2 involved in the recognition of *C. acnes*.[78] As previously stated, inflammation is, indeed, a major contributor to the occurrence of acne in adults.

Combined agents, such as adapalene/benzoyl peroxide, as well as clindamycin/benzoyl peroxide, are increasingly prescribed, as they are instrumental in reducing bacterial resistance. Most topical agents are available in different strengths, formulations, and delivery systems, to be applied in accordance with each individual patient's skin texture.

Azelaic acid 15% gel contains an anti-inflammatory depigmenting active ingredient with antimicrobial and keratinization-normalizing properties. Its antimicrobial effects may be explained by its inhibition of bacterial protein synthesis, in a dose- and pH-dependent manner. This agent was additionally shown to reduce the expression of Toll-like 2 receptors, blocking the inflammatory process.[78]

Systemic Therapies

For patients with moderate to severe acne, displaying insufficient response to combined topical therapy, systemic treatment should be considered.

Oral Antibiotics

When prescribed, limit the duration to 3 months, choosing tetracycline derivatives and consistently including topical benzoyl peroxide during application.[7] The occurrence of treatment failure, especially with oral antibiotics, is widespread in adult women.

Hormone Therapy - Oral Contraceptives and Spironolactone

Hormones have been highly effective in AFA patients, even in those without any changes in serum hormone levels. Hormonal therapies, particularly those consisting of an association of estrogen and new antiandrogenic progestins, can be

used by women who desire contraception, yet without displaying any contraindication to their use.[79] These oral contraceptives lead to a decrease in gonadotropin release, thereby resulting in a diminished ovarian production, along with an anti-androgenic effect on sebaceous gland receptors.[80] In most cases, this results in a clear improvement of acne.

A significant change concerning the manufacturing of combined oral contraceptives consisted in altering their progestin generation content. Consequently, the most recent generation, including drospirenone or chlormadinone, exhibits antiandrogenic activity, along with a better tolerability. On using these new-generation combined oral contraceptives, the incidence of venous thromboembolism has been dramatically decreased, without being totally absent. In addition to venous thromboembolism, the other unwanted effects associated with their use have included nausea, headache, breast pain, intermittent bleeding, and diminished libido, with differing incidence rates, depending on the precise combination employed.[29]

After careful selection of patients, using combined oral contraceptives provides major benefits, in addition to acne improvement. In fact, most of these women experience a reduction in their dysmenorrhea, characterized by frequent menstrual cramps and pain during menstruation.[81]

According to the dictum *primum non nocere* (do no harm), healthcare providers must conduct a careful anamnesis, including family history and smoking habits, before prescribing combined oral contraceptives to women for their acne management. In all women with a high risk of deep venous thrombosis and cardiovascular illnesses, such a prescription is contra-indicated, and must be avoided by all means. Other alternative solutions must be searched for.

Spironolactone is an aldosterone antagonist with anti-androgenic activity, which been shown to diminish sebum production, thereby improving acne lesions.[82] This drug acts fundamentally on the sebaceous glands as an androgen receptor blocker. Generally, the starting dose should be around 100mg per day and it can be divided into two doses, always after a meal. The medication should be administered for a minimum of 6 months before initiating any dosage reduction. Adverse effects are infrequent and manageable, with menstrual irregularities being the most prevalent. The drug is teratogenic, so contraceptive measures must be taken.[82]

Oral Retinoids

Oral isotretinoin is the only treatment that affects all four major factors involved in the development of acne.[83] The recommended starting dose is 0.3–0.5mg/kg/day, which is then gradually increased, depending on clinical response and undesirable effects. Minor unwanted effects include dryness and soreness of eyes, skin, and nasal mucosa.[2] The drug can only be prescribed by dermatologists, and the patient must follow a pregnancy prevention program during and 4 weeks after treatment discontinuation. As acne in adult women is a chronic disease, maintenance treatment, even after the use of oral isotretinoin, should always be prescribed.

Procedural Therapy

The indications for procedural therapy in AFA patients are as follows: predominant comedonal acne, recalcitrant acne, or nodulocystic acne when isotretinoin is either associated with acne flare-ups or contra-indicated. Procedural therapy is primarily aimed at preventing scarring by decreasing inflammation in a faster manner, thus resulting in quicker outcomes, meaning rapid lesion resolution. Comedone extraction is associated with a quick clearance of comedones, with faster skin improvement. Chemical peeling agents, including salicylic acid, mandelic acid, glycolic acid, as well as retinol peels, may prove useful adjuncts in active acne, given that they display comedolytic, keratolytic, and anti-inflammatory properties, while glycolic and retinol peels exhibit the added advantage of targeting pigmentation scars and photoaging.[26] Laser and light therapy may be considered an adjunct to topical and oral drugs, being devoid of major undesirable effects. It must, however, be noted that a recent Cochrane review on light therapies focused on acne concluded that larger studies with improved quality would be required to confirm the long-term benefits of laser intervention in AFA, particularly regarding the high costs of these therapies.[84]

Dermocosmetics in Adult Female Acne Management

Dermocosmetics are skin care products with sophisticated active ingredients that are specifically designed to alleviate symptoms of various skin conditions and preserve or restore a healthy skin barrier physiology. Daily skin care using

dermocosmetics plays an integral role in the holistic management of adult female acne. Specific dermocosmetics have been designed and further adapted to managing acne in view of optimal results.[85] These novel skin care products have undergone rigorous clinical testing, demonstrating their efficacy and safety. Another major advantage of these dermocosmetics is their synergic action mechanism when given as adjunct to pharmacological regimens.[86] These skin care solutions have been primarily designed to attain optimal outcomes, meaning recovery of acne lesions, while improving adherence to treatment, minimizing the occurrence of unwanted effects, and offering additional benefits in terms of skin health and patients' concerns.

Recently, plant-derived bioactive agents have been included in dermocosmetic formulations. The outcome is an extensive portfolio of innovative products with an expanded range of benefits, additionally including anti-acne, anti-aging, antioxidant, hydrating, and depigmenting properties. Below, we provide just a few examples of the enormous progress made in cosmetic research over the last decades, given that a full review on dermocosmetics in the field of acne is scheduled to be published shortly.

Anti-Acne Properties

A skin care product containing *Myrtus communis* extract and azelaic acid, dedicated to AFA, was developed. In a multicenter, randomized, investigator-blinded trial, the efficacy and safety of this test product in acne maintenance phase was compared versus light moisturizing cream (LCM) in 26 test and 27 control subjects, respectively.[87] The products were applied twice daily on the whole face, for a study duration of 16 weeks, with subjects evaluated every 4 weeks. The efficacy was evaluated by means of the number of acne relapses and the investigator's global assessment (IGA). Data analysis revealed that the number of acne relapses was more than double in the comparator group versus the product test group, eight and three, respectively. There was no statistical difference in the mean IGA evolution from baseline between the two groups. Nevertheless, in the product test group, 85% of subjects were assessed as clear or almost clear versus only 67% in the comparative group. According to the authors, these efficacy results after a 16-week trial period suggested a trend towards acne relapse limitation by the test product, along with a benefit in maintaining long-term remission.[87]

Silybum Marianum Fruit Extract Application

Lipid droplet proteins were reported to be involved in the pathogenesis of acne,[88] because they are known to control the levels of comedogenic free fatty acids. Comedoclastin™ is derived from milk thistle seeds (*Silybum marianum L.)*. Dosed in very high concentrations, it helps reduce existing imperfections, while soothing the transformation of micro-comedones, thereby limiting the occurrence of new ones. By this means, this agent breaks the vicious circle that underlies skin impurities, and leaves the skin lastingly clearer.[89] *Silybum marianum* fruit extract application over 48 weeks was reported to significantly decrease free fatty acid release from sebum triglycerides.[88] Based on this observation, this dermocosmetic is likely to be instrumental in maintaining low comedogenic sebum and acne-prone skin health.

Retinaldehyde

Retinaldehyde, also known as retinal, is a vitamin A derivative, which is a well-known ingredient of skincare products, on account of its anti-aging benefits. This agent has also been useful in treating acne.[89,90] It is a milder alternative to retinol, offering similar benefits without the harsh side-effects that some people may experience with retinol.

One way that retinaldehyde may help treat acne is via diminished sebum production by stimulating the production of enzymes that break down sebum.[91] Retinaldehyde may likewise be instrumental in acne management by reducing the acne-associated inflammation via the stimulation of anti-inflammatory protein production. Retinaldehyde has likewise been shown to improve the skin barrier function by stimulating the production of new skin cells. A healthy skin barrier can help prevent bacteria from entering the skin and causing acne.

Protecting the Skin Barrier

Disruption of epithelial skin barrier can constitute a feature related to acne.[92] Yet, this epithelial dysfunction can also be explained by aggressive acne treatments, such as over-The-counter products or harsh peeling procedures. In clinical

terms, skin barrier dysfunction manifests as skin dryness and irritation in the form of burning or tingling. These symptoms are, at least to some extent, accounted for by transepidermal water loss. Accordingly, using moisturizers provides important benefits in acne management.[93]

Active ingredients, including panthenol, ceramides, glycerin, niacinamide, as well as thermal spring water, act in this way. Keratolytic agents, including alpha hydroxy acids, likely support the epithelial barrier function by increasing epidermal thickness and further controlling hyperkeratinization.[91]

Enhancing Microbiome Diversity

The proliferations levels of *C. acnes* have been found to be rather similar between acne patients and healthy subjects, but it is the loss of microbial diversity and the lack of balance between *C. acnes* phenotypes that is typically found in acne patients.[64] This loss of balance results in the colonization of certain *C. acnes* strains, particularly the phylotype $1A_1$. This specific phylotype is particularly common in acne patients, and it has been proven to be able to enhance skin inflammation by activating the innate immune system.[94] Cosmetics targeted at restoring skin microbiome homeostasis may contribute to improving acne patient outcomes. Studies are already underway, and their results will be presented in another review paper.[95]

Improving Pigmentation and Photo-Aging

Postmenopausal women are more susceptible to facial aging due to a shift in hormonal balance and decrease in collagen synthesis. In a prospective randomized double-blind controlled trial involving 44 postmenopausal women, soy proteins containing isoflavones were shown to improve facial signs of photoaging and skin hydration in this patient population.[96] In their conclusion, the authors stated that dietary soy protein supplementation with isoflavones may improve skin photoaging, including wrinkles and dyspigmentation.

Currently, it is well recognized that ultraviolet light (UVA) generates reactive oxygen species that are responsible for skin photo-ageing. A randomized, double-blind, intra-individual controlled monocentric study investigated the in situ antioxidant activity of a dermocosmetic product in photoaged skin.[97] Twenty healthy volunteers had defined skin areas randomized to receive a topical product containing three antioxidants (pre-tocopheryl®, retinaldehyde and glycylglycine ole-amide). Data analysis confirmed the benefits of the topical application of this 3-antioxidant-product in preventing UVA-induced oxidative damage.[97] Additionally, retinoids like retinaldehyde that display anti-acne properties have likewise been shown to display beneficial effects in photo-aging.[97–99]

Recently, increasing evidence has been made available indicating that blue light (BL), particularly high-energy visible (HEV) light (400–450nm), can cause skin damage and pigmentation.[100] In an in vitro study, the BL photostability and photoprotection properties of nine sunscreens containing the broad-spectrum UV/BL phenylene bis-diphenyltriazine (PBDT or TriAsorB™) filter, together with three other organic UV filters, were evaluated.[100] Data analysis revealed all PBDT-containing sunscreens were effective at absorbing BL radiation in vitro. The two representative broad-spectrum sunscreens tested in subjects significantly reduced BL-induced immediate skin pigmentation. Conclusively, effective sunscreens likely offer photoprotection beyond ultraviolet (UV) radiation, thereby preventing or limiting BL-induced cutaneous effects.

Impact of Menopause on Adult Female Acne

Hormonal Dynamics

Menopause, which generally sets in between the ages of 45 and 55 years is characterized by falling estrogen levels. This low-estrogen state exerts a major impact on both skin structure and function.[101] Estrogen receptors are found throughout the skin, with their highest density seen in the face, genital area, and legs.[102] During menopause, dermal collagen is quickly lost, with around one-third collagen lost during the first five post-menopausal years. In parallel, during menopause, elastin degeneration is enhanced, manifesting itself as slack skin and augmented wrinkling. In addition, the barrier function of the skin gradually deteriorates, which is followed increased transdermal water loss. This is thought to possibly initiate the inflammatory cascade in acne, with inflammatory areas detected not only in typical skin lesions, but also in the perilesional areas.[103]

Several factors have been reported to initiate or aggravate AFA that are also likely to contribute to menopausal acne, including cosmetics, dietary habits, stress, and sleep deprivation. In a, study involving 280 adult acne patients, exposure to sunlight was responsible for acne aggravation in 93 (33%) patients, cosmetics in 40 (14%), and stress in 72 (26%).[26] A number of patients displayed comorbidities in addition to acne, such as obesity and hirsutism, each in 6%, and alopecia in 2% patients. Yet, it should be noted that increased testosterone levels were observed in only seven (3%) among the 230 female patients participating in the survey. Other authors have distinguished a number of differentiating features between acne in adults before and after menopause, which are listed and detailed in Table 1.[26]

Management Strategies

During menopause, numerous skin changes occur, with major loss of skin collagen, and reduced elasticity, manifesting as dry and itchy skin, wrinkles, and possibly acne. The approach to treatment of menopausal women can be challenging. Most anti-acne products have been designed for adolescents, affected by oily skin, with much fewer anti-acne products designed for adult and post-menopausal sensitive mature skin. While the therapeutic objective is to improve acne and its sequelae, including hyperpigmentation and scaring, irritation to the aging skin must be avoided by all means. Skin care is particularly essential during this transition period, and skin care products must be selected with great attention to protect the aging skin.[26] The face must be washed daily using a syndet cleanser respecting the skin's physiological pH. However, frequent face washings, as well as scrubs, are contra-indicated, as they are likely to aggravate skin dryness and irritation. Patients should be advised not to pick at acne lesion, as this can exacerbate inflammation and eventually result in infection. The moisturizer to be applied should be noncomedogenic and must be used prior to other topical agents.[26] Water-based cosmetics are to be preferred, with all makeup carefully washed off prior to bedtime.

Topical treatment constitutes the backbone of current therapeutic strategies, and these topical products must be applied for a prolonged period of time. Their judicious use has been linked with improved treatment adherence and superior patient satisfaction. Moreover, these topical therapies have been associated with benefits regarding concomitant

Table 1 Characteristics of Adult Female Acne (≥25 Years Old)

	Before Menopause	**After Menopause**
Prevalence	20–40%	15.3% (in their 50's or older)
Hormonal changes	Most patients do not exhibit detectable hormonal changes in laboratory assessments	Menopause is associated with a decline in estrogen levels and an imbalance with androgens
Collagen loss	Around 20% (on average up to 45 years old)	More than 50% (over 50 years) (Menopause is associated with a decline in collagen production, contributing to skin thinning and making it more prone to scarring from acne lesions)
Hirsutism	Rare	Not rare (related to postmenopausal hyperandrogenism – decreased SHBG)
Typical location	Cheeks, around the mouth, lower chin (U-zone)	Cheeks, around the mouth, lower chin (U-zone)
Morphological characteristics	Two clinical profiles: • Hyperseborrhea, non-inflammatory lesions • Superficial inflammatory lesions, deep seated nodules and cysts	• Deep-seated inflammatory papules or nodules with a predominant perioral distribution Multiple closed comedones visible on stretching the skin, with enlarged pores in nasal and malar areas
Severity	Mild-to-moderate	Mild-to-moderate
Duration	Chronic duration	Chronic duration
Skin type	Normal to oily skin	Normal to dry skin
Skin sensitivity	Affected by skin aging process	Affected by skin aging process
Impact on quality of life	Greater impact than on younger people; affects self-esteem and body satisfaction	Greater impact than on younger people; affects self-esteem and body satisfaction
Skin care	Must always be associated	Must always be associated
Topical therapy	Intended for the treatment of acne and its consequences	Intended for the treatment of acne and its consequences but also to improve concomitant signs of photoaging that are common in this group
Oral therapy	Combined oral contraceptives are an option	Combined oral contraceptives are not an option

Note: Adapted according to Khunger and Mehrotra[26] and Layton AM, Dias da Rocha MA.[98]

signs of photoaging.[26] In many cases, combination therapies with topical benzoyl peroxide, retinoids, azelaic acid, or salicylic acid are recommended to be employed as first-line therapies, depending on the patient's skin lesions, skin texture, and skin tolerability.[26]

Systemic therapy, mostly in combination with topical products, may at times be required, if acne turns out to be deep-seated and therapy-resistant.

Conclusions

The chronic characteristics of AFA require treatments for both the acute and maintenance phases. We know that the skin changes according to the stages of life and that menopause strongly influences this process. Therefore, we must be aware of all these factors, selecting the best therapeutic strategies available for each life period, not only with medications but also through the associated use of dermocosmetics including an adapted photoprotection, targeting the active lesions, as well as associated dyschromia and photo-aging.

Patients Consent Statement

Patients provided written informed consent for their images to be published.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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MADR received fees related to classes and the advisory board from Pierre Fabre, FQM, Galderma, L'Oreal, Naos Group, Kenvue, Johnson&Johnson, Hypera and Dove-Unilever. EB received fees related to classes and the advisory board from Pierre Fabre, L'Oreal, FQM, Pechoin, and Allergan-AbbVie. MSA, VM, FC, GD, and AC are employees of Pierre Fabre. The authors report no other conflicts of interest in this work.

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