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The Pathogenesis and Management of Acne-Induced Post-inflammatory Hyperpigmentation

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REVIEW ARTICLE

The Pathogenesis and Management of Acne-Induced Post-inflammatory Hyperpigmentation

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Abstract
Acne vulgaris is a common inflammatory disease. Among patients with darker skin phototypes (Fitzpatrick III–VI), the inflammatory processes of acne stimulate excess melanogenesis and abnormal melanin deposition, leading to pigmentary sequelae known as post-inflammatory hyperpigmentation and post-inflammatory erythema in all skin tones, although post-inflammatory hyperpigmentation is more common in darker skin and post-inflammatory erythema in lighter skin. These pigmentary alterations can be long lasting and are often more distressing to patients than the active acne lesions. This article discusses what is known about acne-related pigmentation, much of which is extrapolated from general study of nonspecific pigment deposition. Because dyspigmentation poses both a significant clinical concern to patients and a therapeutic challenge to clinicians, we formed a working group consisting of pigmentary experts with the aim of increasing awareness and education of acne-related pigmentary sequelae.

Key Points

Pigmentary deposition is an important problem for acne patients, particularly those with darker skin.

Preventing the development of PIH during the inflammatory acne phase is a key strategy.

1 Introduction

Acne is one of the most common dermatologic diseases across all racial and ethnic backgrounds. For many patients, it is often accompanied by pigmentary sequelae, including post-inflammatory hyperpigmentation (PIH) and post-inflammatory erythema (PIE) [1–4]. Acne-associated PIH occurs most commonly in individuals with darker skin (Fitzpatrick skin phototypes IV–VI), with reported ranges from 45.5 to 87.2%, and both acne and associated dyschromias rank among the chief complaints that bring patients

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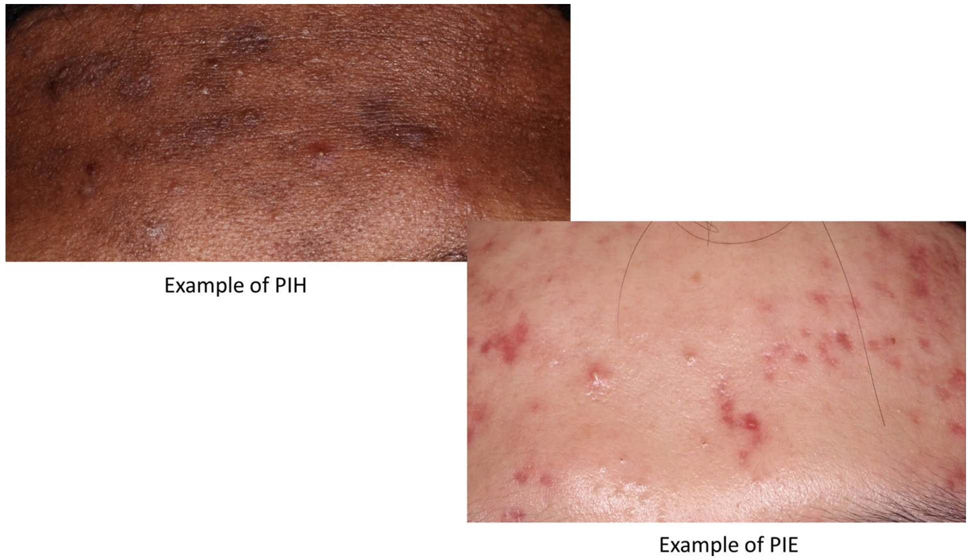


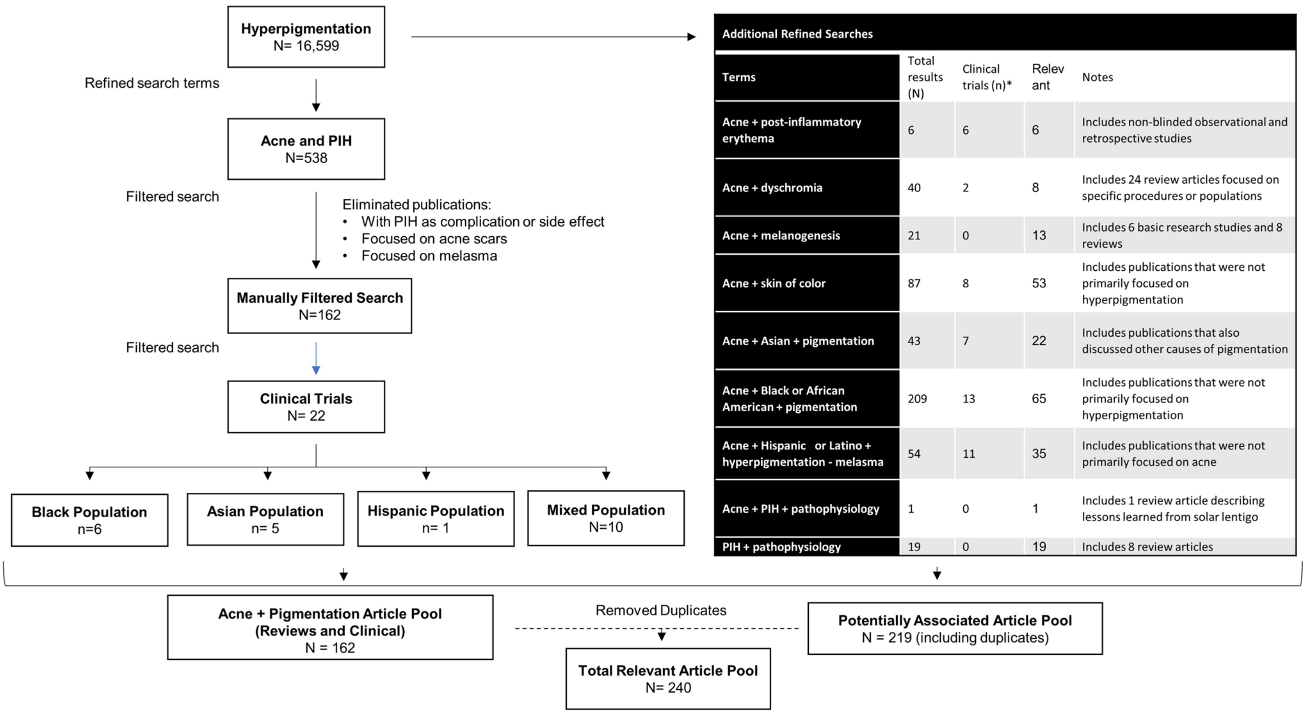
Fig. 1 Clinical photos illustrating color differences between post-inflammatory hyperpigmentation (PIH) and post-inflammatory erythema (PIE). Courtesy of Galderma Laboratories, LP

with skin of color to dermatology offices [5–11]. Although there are no standard criteria distinguishing PIH from PIE, many clinicians associate PIH with brown-to-violaceous tones and PIE with pink-to-red tones (Fig. 1) [5, 12, 13]. In addition, some clinicians are more likely to use the term PIE in cases where there are still active acne lesions intermingled with skin dyschromia [5]. As noted by Goh et al., PIH and erythema are often present together, which can pose a challenge when diagnosing and communicating about acne-related PIH [6].

For many acne sufferers with darker skin tones, PIH is at least as concerning as the acne lesions themselves and in many cases is considered even more troublesome than the acne [14]. Acne-associated PIH has been shown to affect quality of life; in a cross-sectional survey of 200 patients, acne-related PIH was associated with diminished social life, avoidance of public facilities, poor body image/self-esteem, and a perception of more severe disease [5, 15, 16]. Recent studies have indicated that acne-related pigmentation is frequently long lasting [5, 16]. In a Southeast Asian population, 58.2% of patients reported PIH to have been present for more than 1 year and 22.3% reported dyschromia persisting for ≥ 5 years [5]; similarly, 52.6% of patients with acne in the Middle East reported that PIH had been present for at least 1 year [16]. Modifiable risk factors for acne-related pigmentary problems have been identified, and include delays in seeking treatment for acne and excoriation of acne lesions [5, 8, 17, 18]. However, in patients with acne and in comparison to PIH as a result of other causes, the literature regarding acne-associated PIH remains sparse particularly in regard to the condition's pathogenesis and management. This article summarizes current knowledge and identifies areas of future study that could be clinically beneficial.

2 Methods of Literature Review

A review and analysis of the medical literature were conducted using the National Library of Medicine's PubMed database. The search was initiated with the string: ("PIH") or ("hyperpigmentation") or ("postinflammatory") or ("post-inflammatory") or ("postinflammatory hyperpigmentation") or ("post-inflammatory hyperpigmentation") and "acne;" this yielded a total of 538 studies (Fig. 2) and included publications from 1985 to 2021. These were individually reviewed for relevance; publications with PIH as a complication or a side effect and those focused on acne scars or melasma were eliminated. A total of 162 publications remained that were judged directly relevant to the topic of acne and PIH; the PubMed filter for clinical trials was applied, resulting in 22 publications. The 22 clinical trials were further evaluated to determine the population studied, resulting in six publications with African American/Black subjects, five with Asian subjects, one with a Hispanic population, and ten with mixed populations. The same search logic was applied for the terms in the tabular portion of the figure; each search result was manually reviewed for relevance to this publication and any duplications between search results were removed.



Terms	Total results (N)	Clinical trials (n)*	Relevant	Notes
Acne + post-inflammatory erythema	6	6	6	Includes non-blinded observational and retrospective studies
Acne + dyschromia	40	2	8	Includes 24 review articles focused on specific procedures or populations
Acne + melanogenesis	21	0	13	Includes 6 basic research studies and 8 reviews
Acne + skin of color	87	8	53	Includes publications that were not primarily focused on hyperpigmentation
Acne + Asian + pigmentation	43	7	22	Includes publications that also discussed other causes of pigmentation
Acne + Black or African American + pigmentation	209	13	65	Includes publications that were not primarily focused on hyperpigmentation
Acne + Hispanic or Latino + hyperpigmentation - melasma	54	11	35	Includes publications that were not primarily focused on acne
Acne + PIH + pathophysiology	1	0	1	Includes 1 review article describing lessons learned from solar lentigo
PIH + pathophysiology	19	0	19	Includes 8 review articles

Fig. 2 Flow chart showing the literature search query strategy. *PIH* post-inflammatory hyperpigmentation

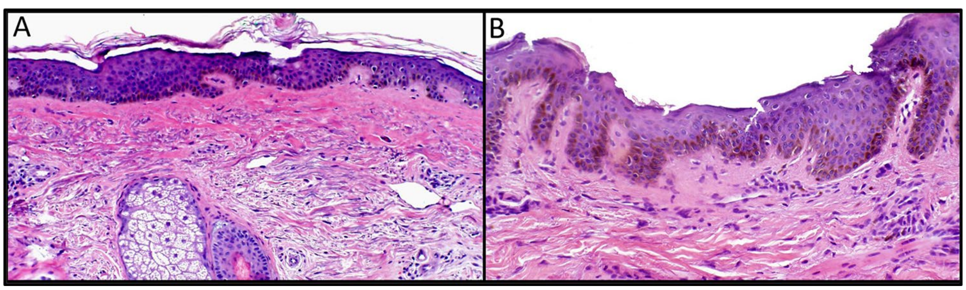


Fig. 3 Post-inflammatory hyperpigmentation. Normal (**A**) and post-inflammatory hyperpigmentation involved (**B**) skin sections (10× magnification, hematoxylin and eosin staining). Photographs courtesy of Pearl Grimes, unpublished histological study of post-inflammatory hyperpigmentation

3 Results: Current Understanding of the Pathogenesis of Acne-Associated PIH

3.1 Acne and Inflammation

In acne-related PIH, it is believed that acne-associated inflammation stimulates melanogenesis and resultant pigment deposition (Fig. 3) [19]. Over the past decade, increasing evidence has pointed to a role for inflammation at all stages of acne, even at the subclinical level prior to formation of comedones [20, 21]. A lymphocytic perivascular infiltrate has been identified in acne lesions just 6–72 h old, including lesions identified as microcomedones, evidence that inflammatory events occur very early in the development of acne lesions [22]. A study of uninvolved skin has suggested that inflammatory events may also occur before initial hyperproliferative changes [21]. The exact signaling pathways of acne-related inflammation are not yet completely understood; however, potential early sources of inflammation include sebum dynamics and the innate immune response to *Cutibacterium acnes* [20].

3.2 Acne, Inflammation, and Pigmentation

As noted in Sect. 3.1, acne-associated inflammation has a marked impact on pigment-producing melanocytes; thus, it seems reasonable that reducing inflammation at the cellular level can reduce the likelihood of pigment deposition [19]. The inflammatory process of acne stimulates melanocytes to over-produce or irregularly disperse melanin [19, 23]. While the exact pathogenesis of acne-related PIH is incompletely understood, it is thought that the release of arachidonic acid in response to epidermal inflammatory events leads to oxidation of prostaglandins, leukotrienes, and other molecules that stimulate melanocyte activity [24]. As more melanin is synthesized, more pigment is distributed to keratinocytes [24, 25]. Generally, it is believed that the intensity of pigmentary response correlates with the degree of inflammation and long-term and/or relapsing inflammation [26]. However, to date, there are no validated outcome measures or imaging techniques available for clinical or research use.

There are few data to inform clinicians about whether acne-related PIH differs from PIH associated with other causes in any physiologic aspects. In 2015, Isedeh and colleagues validated an in vivo model for PIH using exposure to 35% trichloroacetic acid to induce pigmentation [27]. An 8-week pilot study comparing the trichloroacetic acid-treated sites with PIH associated with acne lesions showed that while the initial phases of inflammation were different between the two types of pigmentation, similar clinical evaluations were made for the two types of lesions starting at day 14. Colorimetry, spectroscopy, and histologic data were also collected, and by day 28 were comparable for the two types of PIH [27]. The availability of a viable model will help future researchers better understand the condition and its management.

In acne, PIH manifests as localized or diffuse brown-to-gray brown macules at sites of acne lesions and becomes most apparent after lesional erythema has resolved [6]. Post-inflammatory hyperpigmentation may also appear violaceous, and that may be a sign of resolving acne where inflammation is contributing to the violaceous discoloration more than brownish pigment. In darker skin, erythema may not be as visible and the only clinical sign of inflammation may be a more subtle violaceous hue, an important consideration in management decisions. Because acne-associated pigmentation tends to be long lasting, many patients desire a management approach that focuses not only on resolving acne lesions but also on reducing dark spots and improving overall skin coloration.

The localization of pigment in either the dermis or epidermal layer of the skin affects both the resultant color and response to treatment [19, 28]. Post-inflammatory hyperpigmentation can be due to overproduction of melanin or irregular deposition of pigment after cutaneous injury or inflammation; in addition, the process can involve increased melanin production by existing melanocytes or by increased proliferation of active melanocytes [26, 29]. Acne-related PIH typically involves the epidermis, as melanocytes transfer melanin to surrounding keratinocytes (Fig. 4). Melanin synthesis takes place within specialized membrane-bound organelles known as melanosomes, and involves the creation and exportation of structural proteins from the endoplasmic reticulum and bonding of the proteins with regulatory glycoproteins that are specific to the melanosome [30]. The

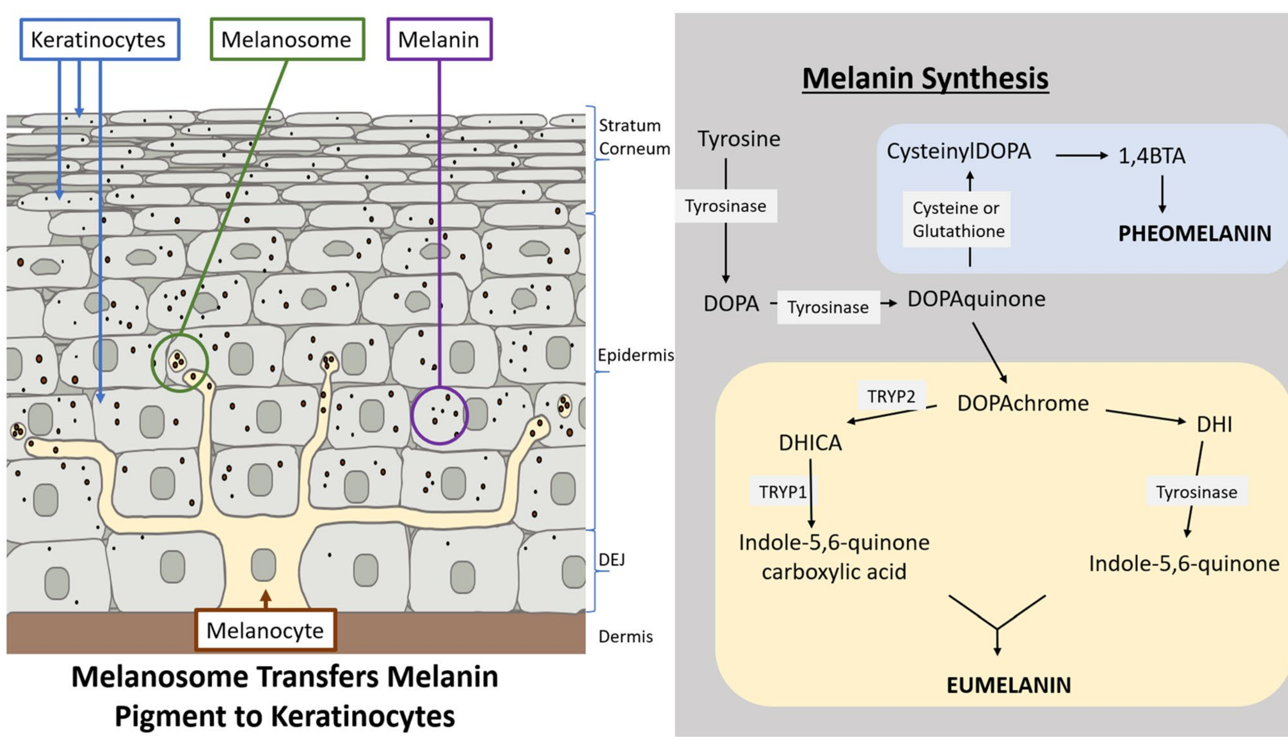


Fig. 4 Schematic of melanocyte transfer of melanin to keratinocytes in the epidermis. *BTA* benzothiazinyl-alanine, *DEJ* dermoepidermal junction, *DHI* 5,6-dihydroxyindole, *DHICA* 5,6-dihydroxyindole-2-carboxylic acid, *DOPA* dihydroxyphenylalanine, *TRYP* tyrosine-related protein

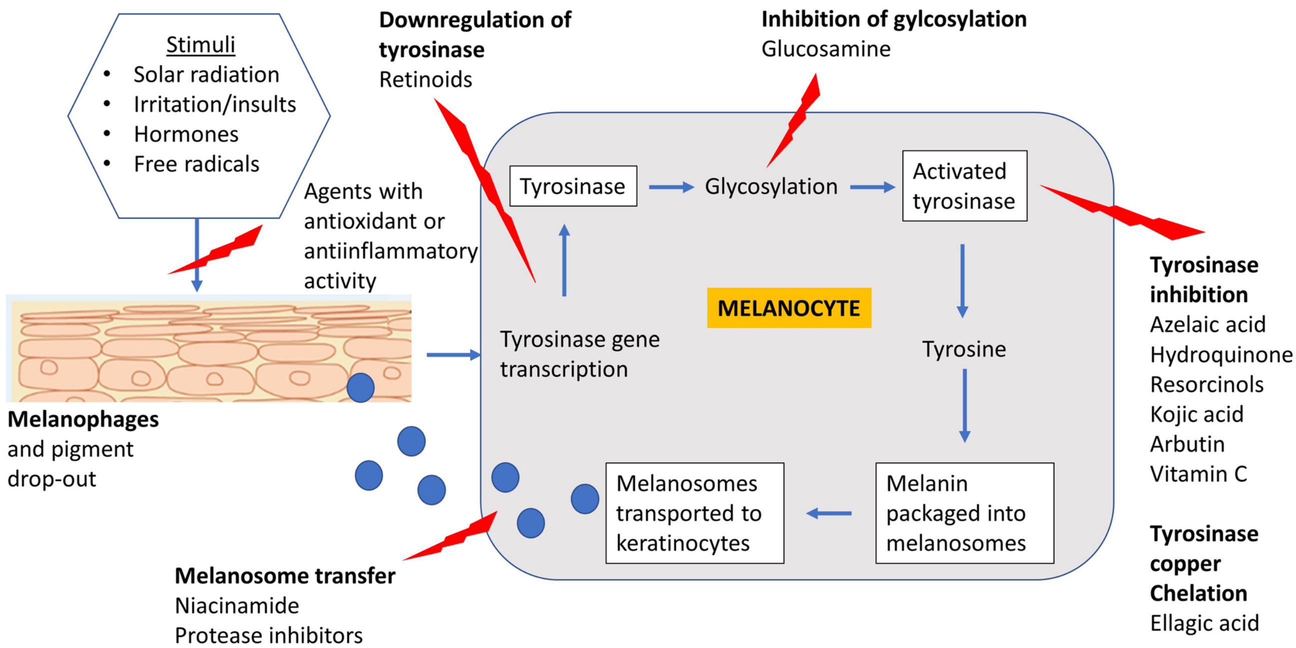


Fig. 5 Cycle of tyrosinase activation in response to stimuli

complex process of melanin synthesis is regulated by the sorting and trafficking of protein complexes to the melanosome [26]. Melanocytes reside in the basal epithelial layer above the dermal-epidermal junction and interact with multiple keratinocytes to transfer melanosomes as needed to protect the skin [30]. A rise in melanocyte activity can be stimulated by prostaglandins, cytokines, chemokines, and additional inflammatory mediators such as reactive oxygen species [26].

Less frequently, dermal pigment deposition occurs after adjacent keratinocytes are damaged by inflammation and release large quantities of melanin [19]. Free pigment is scavenged by melanophages (a macrophage) in the upper dermis, contributing to a blue-gray appearance to the skin [19].

The process of melanogenesis, both in general and in acne-related PIH, is driven by the enzyme tyrosinase (Fig. 5) [29]. Perhaps not surprisingly, then, the tyrosinase pathway is a target for many of the treatments that have been shown effective in reducing acne-related PIH. Tyrosinase catalyzes the two major forms of melanins: black/brown eumelanin and yellow-red pheomelanin [29]. Microphthalmia transcription factor is a "master regulator of melanocyte development, function, and survival" [30] and regulates transcription of tyrosinase and its targets tyrosinase-related proteins [31, 32]. This may also potentially pose a target for therapeutic intervention.

4 From Bench to Bedside: Managing Acne-Associated PIH

4.1 General Measures

Although acne-associated PIH is a common problem, much of what is known about correcting pigment alteration comes from melasma studies; going forward, it will be important to conduct randomized controlled clinical trials in acne-associated PIH to help guide clinicians in therapeutic decisions. At present, general management strategies start with treating acne as effectively and aggressively as possible without having the treatment to contribute to additional irritation or inflammation [33]. However, in part because of the relatively limited treatment options for PIH, it is important to counsel patients on methods to prevent further discoloration of skin, such as regular use of sunscreen, protective clothing, and sun avoidance; this may be particularly important for those with darker skin tones, who may not normally practice photoprotection [19]. It is also important to educate patients about not manipulating or excoriating acne lesions, as this can prolong pigmentation. Good-quality photos or other imaging can be helpful to counsel patients about efficacy.

4.2 Therapeutic Approaches

4.2.1 Medical Therapies

As shown in Table 1, medical therapies can correct hypermelanosis by acting at various steps in melanogenesis,

Table 1 Mechanisms of depigmenting agents

Stage of melanin synthesis	Depigmenting agents
Interrupting irritant-induced melanogenesis	Antioxidants: ascorbic acid, alpha-tocopherol, 6-hydroxy-3,4-dihydrocoumarin, resveratrol, alpha-lipoic acid
Interfering in the tyrosinase pathway	Inhibition of tyrosinase activity: arbutin, ascorbic acid, azelaic acid, hydroquinone, kojic acid, 4-n-butylresorcinol, licorice extracts, topical retinoids Reduction in tyrosinase production: ceramide, sphingosine-1-phosphate Increase of tyrosinase degradation: hydroquinone, linoleic acid, linolenic acid, oleic acid
Inhibiting melanosome transfer/maturation	Niacinamide, lectins, neoglycoproteins, arbutin, soy trypsin inhibitor
Inhibiting UV plasmin-induced activity in keratinocytes	Tranexamic acid
Increasing epidermal turnover	Procedures, topical retinoids

UV ultraviolet

melanin transfer, and even in the processing or degradation of melanin [29, 34]. Topical treatments fade excess pigment, block pigment formation, accelerate skin cell turnover rate, or work through a combination of these actions. Treatments that fade excess pigment or block pigment formation include hydroquinone (HQ), kojic acid, retinoids, and azelaic acid, while those that increase skin turnover include retinoids. Topical treatments are generally utilized for epidermal pigmentation, but not for dermal pigmentation because of a reduced response in the deeper tissue [19].

Hydroquinone, a common treatment for PIH, is a tyrosinase inhibitor that blocks the conversion of melanogenic precursors. It may also inhibit transcription and expression at the genetic level, may be cytotoxic to melanocytes, and may increase the degradation of melanosomes [35]. According to Davis and Callender, HQ monotherapy can reduce pigmentation, but newer formulations combining HQ with additional agents, such as retinoids, corticosteroids, glycolic acid, antioxidants, or sunscreens, have shown better efficacy compared with monotherapy [19]. At concentrations of 4% and higher, irritation can occur with HQ; adding a topical corticosteroid reduces this irritation and enhances depigmenting ability [19]. A triple combination of HQ, a retinoid, and a corticosteroid (compounded and known as the Kligman-Willis formula) has shown to be effective but irritating; more recently, a less-irritating commercial formulation was approved for the treatment of melasma, which contains 4% HQ, 0.05% tretinoin, and 0.01% fluocinolone (TriLuma; Galderma, Fort Worth, TX, USA) [19]. In some settings, concern about steroid-induced acne may limit the use of triple combination therapy in acne. This formulation, which is not approved for the treatment of acne-related PIH, has shown to be both safe and effective for melasma and photoaging, and successfully used clinically to manage PIH [19]. More formal study is needed to better define its role in acne-related PIH. Retinoids increase skin cell turnover, have anti-inflammatory properties, and can induce apoptosis, all of which can contribute to skin lightening [19]. Azelaic acid exerts depigmenting actions by inhibiting tyrosinase and through selective cytotoxic effects on abnormal melanocytes [19]. Kircik reported positive results with azelaic acid in a small exploratory study [36]. Most studies of the depigmenting effects of azelaic acid have been in melasma, and as with other agents, more formal study in acne-related PIH is warranted. With many medical therapies, it is important for the clinician to be mindful of the potential of treatments to cause or exacerbate PIH due to irritation.

4.2.2 Procedures

Adjunctive therapies, such as chemical peels, lasers, and microneedling, can enhance efficacy. Superficial peels (including glycolic acid, salicylic acid, and Jessner solution) have been used safely across skin types for PIH but lasers are typically reserved for lighter skin types. Microdermabrasion and non-ablative lasers have been used to reduce pigment alterations, but may not be well suited for patients who have active acne. Generally, these approaches work in acne-related PIH by increasing epidermal turnover and promoting re-epithelialization with less pigmented cells [37]. Procedures are accompanied by the risk for creating PIH complications, with the greatest risk among darker skinned individuals (phototypes IV–VI). In a study of Asian patients treated with laser skin resurfacing, Chan et al. reported that the density and energy of the laser treatment both contribute to the risk of PIH in dark-skinned patients [38]. The same authors noted that prevention of bulk tissue heating is also important with laser use, particularly when applied to small anatomical areas [38–41]. As early as 2013, Alexis published a review of laser and light-based modalities suitable for darker skin types, noting that while early devices were associated with a relatively high rate of unacceptable side effects, the technology had evolved significantly allowing more widespread use in this population. In 2020, a retrospective chart and photographic review showed two or more treatments with a low-energy/density, non-ablative, fractional 1927-nm wavelength laser improved PIH by a mean of 43% with no significant side effects, indicating the benefits that can be achieved with a procedural approach [40]. Peels and microneedling can also induce pigmentation and should be used with care in people with dark skin tones [30].

5 Conclusions

Acne-related PIH is a common sequelae of acne vulgaris. Its pathogenesis and management remain challenging and relatively poorly understood. To improve management and treatment outcomes, it is important to gain a better understanding of the pathogenesis of acne-associated PIH and to perform well-designed studies to evaluate the efficacy and safety of treatments that target different steps of pathogenesis.

Patients with areas of dyschromia particularly on their face typically feel a significant negative mental and social impact. Managing acne and acne-related PIH can pose a challenge for the clinician, owing to the need to adequately control and treat the process causing the PIH, the length of time needed for pigmentation to subside, the cost of medications, lack of insurance coverage, and the difficulty of treating the PIH without bleaching or damaging the surrounding skin. A primary strategy is to prevent the development of PIH during the inflammatory acne phase. With this and upcoming publications, we hope to increase awareness of the magnitude of the problem and provide guidance on best treatment practices, including potentially helpful combination therapy strategies that can treat acne and PIH concurrently.

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Declarations

Conflict of interest Dr Elbuluk has served as a paid consultant and/or advisory board member for VisualDx, Scientis, Galderma Laboratories LP, Zosana, and Avita; and has received fees for being a Unilever partner. Dr Grimes has served as a consultant for Galderma Laboratories LP, Up-to-Date, and Proctor & Gamble, received grants from Incyte, VT Technologies, Pfizer, Sun, and Arcutis, and has lectures for Scientis (Cyspera). Dr Chien has served as a consultant and/or advisory board member for Galderma Laboratories LP. Dr Hamzavi has served as a consultant and/or advisory board member for Galderma Laboratories LP, AbbVie, Incyte, Pfizer, UCB, Boehringer Ingelheim, and Clarify Medical; he has served as an investigator for Pfizer Inc, Bayer, Lenicura, Incyte, Estee Lauder, Ferndale Laboratories, Inc, Galderma Laboratories LP, L'Oreal, Unigen, Arcutis, and Avita; and is Co-Chair of the Global Vitiligo Foundation. Dr Alexis has served as a consultant and/or advisory board member for Leo, Novartis, Galderma Laboratories LP, Sanofi Regeneron, Dermavent, Unilever, Beiersdorf, Valeant, L'Oreal, Bristol Meyers Squibb, Scientis, Bausch Health, UCB, Arcutis, Janssen, Allergan, Almirall, AbbVie, and Sol-Gel; has served as a speaker for Astra Zeneca; and has received royalties from Springer Verlag, Wiley Blackwell, and Wolters Kluwer. Dr Taylor has served as a consultant, advisory board member, speaker and investigator for Galderma Laboratories LP. Dr Gonzalez has served as a consultant and/or advisory board member for Galderma Laboratories LP, Neostrata, Exuviance, and Bioderma. Dr Weiss has served as a speaker for Abbvie, Almirall, Galderma Laboratories LP, Ortho Dermatologics, Regeneron and Sanofi; as a consultant and/or advisory board member for Cassiopia, Cutera Inc, Dr Reddy, EPI Health, Foamix, Galderma Laboratories LP, Incyte, Leo Pharma, Novartis, Ortho Dermatologics, and UCB; and as investigator for AbbVie, Aclaris, Bausch Health, Celgene/Amgen, Cutera, Endo, Foamix, Galderma Laboratories LP, Leo Pharma, Moberg, and Novartis. Dr Kang has served as a consultant and investigator for Almirall and Galderma Laboratories LP.

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