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Review Article

Expert opinion on current trends in hyperpigmentation management: Indian perspective

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ABSTRACT

Hyperpigmentation is a common pigmentary disorder characterized by increased production of melanin. It is present in Asian skin phototypes, with a higher prevalence in the Indian population. Skin heterogeneity is seen in more than 80% of individuals of all age groups and genders in several cities across India. In children, the prevalence of hyperpigmentary disorders accounts for 1.54 per 1000 children. Sixty expert dermatologists participated in expert group meetings via teleconference webinar to elaborate on the current trends in the management of hyperpigmentary disorders. The major reasons for hyperpigmentary disorders in India include melanocyte function followed by exposure to ultraviolet radiation, race, ethnicity, use of medications, pregnancy, and use of cosmetic. There are wide varieties of skin-lightening or depigmenting agents and skin resurfacing procedures that aid in the management of hyperpigmentation. However, treatment becomes challenging due to compliance issues related to affordability, complexity of prescriptions, and treatment duration. Compliance increases only if the patient sees any improvement or discontinues treatment due to higher expectations. Hence, the success of the treatment lies in patient adherence. This article summarizes expert opinions on identifying, diagnosing, and managing hyperpigmentation with the help of topical depigmenting agents in the Indian scenario. It also emphasizes treatment adherence issues along with the role of patient counseling and education regarding disease awareness and treatment strategies.

Keywords: Hyperpigmentation, Pigmentary disorders, Photoprotection, Patient adherence

INTRODUCTION

Hyperpigmentation is a common dermatological condition where patches of skin become darker in color than the surrounding skin.[1] It is also described as a group of diseases, which can be either congenital with different inheritance patterns or acquired i.e. secondary to cutaneous or systemic problems.[2] The darkening of the skin is attributed to excess melanin, which gets deposited on the skin. It can occur in people of any race and is one of the major skin concerns for people with pigmented skin types especially in the Asian and Indian populations.[3] It is found to be among the top 11 skin conditions seen by dermatologists with 24.7 million visits for the management of change of skin colour.[4] Patients usually develop social and emotional insecurities as they feel embarrassed and

self-conscious, which compels them to avoid social gatherings or change the way they dress.[4] Several studies also report psychological problems that arise due to skin appearance.[5]

Hyperpigmentation comprises three major types in the Indian scenario, namely, post-inflammatory hyperpigmentation (PIH), melasma, and actinic lentigines, with the first two being associated with an increase in melanin production due to multiple factors.[3,4]

Skin heterogeneity is seen in more than 80% of individuals of all age groups and genders in several cities across India.[3,7] In children, the prevalence of hyperpigmentary disorders accounts for 1.54 per 1000 children.[6,8] Other types of hyperpigmentation include periorbital hyperpigmentation, lichen planus, Riehl's melanosis, idiopathic guttate and confluent hypermelanosis, lichen amyloidosis and nevus of Ota, dermatosis papulosa nigra, phytophotodermatitis, flagellate dermatosis, erythema dyschromicum perstans, cervical poikiloderma (poikiloderma of Civatte), acanthosis nigricans, cutaneous amyloidosis, and reticulated confluent dermatitis.[2,3,6] In childhood, the common hyperpigmentary disorders include post-inflammatory hyperpigmentation, café-au-lait macules, pigmentary mosaicism, congenital melanocytic nevi, lichen planus, and Mongolian spots.[6]

Expert group meetings were conducted via teleconference webinar with 60 expert dermatologists across India. The purpose of the meeting was to discuss current clinical evidence on the diagnosis and treatment of hyperpigmentary disorders in India and to gather expert insights on effective diagnosis and management of hyperpigmentation and the role of patient counselling in the Indian scenario.

A literature search was performed using PubMed and Google using Boolean operators and/or for keywords such as hyperpigmentation, pigmentary disorders, melasma, sunscreen, and photoprotection. In this paper, clinical data were obtained from 30 published research articles, systematic reviews, or meta-analyses performed on humans. This article summarizes consensus of expert opinions on epidemiology, causative factors, diagnostic methods, treatment options, and patient counselling in clinical practice. The consensus draft has been formulated with the help of experts' suggestions.

HYPERPIGMENTATION DISORDERS

The common hyperpigmentary disorders observed in India are as follows.[3]

Post-inflammatory hyperpigmentation

Post-inflammatory hyperpigmentation (PIH) is an acquired type of hyperpigmentation occurring due to an inflammatory reaction or skin injury.[2-4,9] It is seen in people with higher skin phototypes due to high melanin content.[2] Some cutaneous conditions such as acne vulgaris, eczema, impetigo, psoriasis, lichen planus, pityriasis rosea, insect bites; or even laser treatment may result in PIH.[2,3] PIH can affect both epidermis and dermis.[9]

Melasma

Melasma or chloasma is one of the most common acquired hyperpigmentary disorders, which affects the facial area. It is characterized by brown to greyish hyperpigmented macules with irregular borders.[2,3,10] It affects the skin exposed to sunlight especially on the face and neck and less commonly on the arms and sternal area.[2,4] The pattern of distribution of melasma can be centro-facial, malar, or mandibular.[2,5] On the face, it mainly occurs on the forehead, cheeks, upper lips, and chin.[5]

Actinic lentigines

Actinic lentigines also termed as solar lentigines are light to dark brown hyperpigmentation spots or uneven patches that occur due to sun exposure.[3,11] Ultraviolet (UV) radiation triggers generation of melanocytes locally leading to melanin accumulation. They can present as single or multiple spots.[3] The sun-exposed areas like the dorsal part of the arms, upper trunk, and also on the face are the most affected.[3,11] They are more frequently observed in adults than in children.[12]

Periorbital hyperpigmentation

Periorbital hyperpigmentation (POH) or dark circles is another frequent dermatological problem that affects individuals of all ages, irrespective of gender or race.[2] It can affect the facial appearance and also influence the emotional wellbeing and quality of life of the individual.[2,13]

Facial acanthosis nigricans (FAN) also known as metabolic melanosis and metabolic melasma, appears as brown to black macular pigments found in zygomatic or malar areas with varying degree of roughness.[14]

The expert panel agreed that the most common hyperpigmentary disorders include melasma, hyperpigmentation secondary to acne, lichen planus, and PIH due to lichen planus pigmentosus (LPP). Among approximately 10 patients who visit the clinic with complaints of hyperpigmentation, 3-4 complain of acne, 3-4 complain of different types of pigmentations, and the remaining 1-2 complain of pigmentations that are difficult to manage.

The panel opined that in children, papular urticaria is most commonly observed. In the past few years, conditions including acne induced hyperpigmentation, paederus dermatitis, acanthosis nigricans, frictional dermatitis, polymorphous pigmentation, cosmetic pigmentation, and hyperpigmentation due to dengue and chikungunya have become more common compared to PIH. Other

inflammatory causes of hyperpigmentation may be skin disorders such as psoriasis, eczema, drug reactions, and nutritional deficiencies. Facial melanosis conditions including erythema dyschromicum perstans (EDP), lichen planus pigmentosus (LPP), Riehl's melanosis (RM), erythromelanosis peribuccale pigmentaire of brocq (EPP), Poikiloderma of civatte, erythromelanosis follicularis of face and neck, nevus of ota, hori's nevus, maturational hyperpigmentation, periorbital hypermelanosis, pigmentary demarcation lines, ephelides, drug-induced pigmentation, Addison's disease, contact dermatitis, photomelanosis, and seborrhoeic melanosis are less common yet debilitating hyperpigmentation disorders encountered in clinical practice. They further added that topical steroid abuse is an important reason for hyperpigmentation. Impetigo and pityriasis are also seen in acute hyperpigmentation cases.

Etiology

The main cause of pigmentation of the skin, hair, or eyes depends on the melanocyte function, and pigmentation results from interaction between epidermal melanin unit, genetic factors, and also due to immunological or toxin-mediated destruction of melanocytes (Figure 1).[6] Various medications like antibiotics, diuretics, pain-killers, and oral contraceptives (OCPs) can stimulate hyperpigmentation.[6] Differences in skin color resulting from racial and ethnic differences depend on endocrine and autocrine factors.[6] UV exposure mostly influences pigmentation of the skin and especially affects fair skin (phototypes I-IV). Melanogenesis occurs after UV exposure, which is stimulated with the help of keratinocytes and fibroblasts.[10] UV-B radiation causes direct damage to the DNA, and UV-A causes the formation of reactive oxygen species that indirectly affect the DNA. It also causes photoaging.[3] Melasma occurs due to the involvement of melanocortin, which is induced by UV radiation.[2] Solar lentigines cause the formation of dark brown spots in response to UV radiation.[11]

Melasma occurs in the presence of biologically active melanocytes on the damaged skin.[9] It is a result of genetic predisposition and also other factors like pregnancy, use of oral contraceptives, endocrine diseases, hormonal therapy, and residing in higher altitudes.[2,5,9] In pregnancy, estrogen triggers melisma, but the pathogenesis of melasma is multifactorial.[4] Studies have reported that 55-64% of individuals with melasma have had a family history of melasma.[10,15,16] Studies indicate that the clinical and histological features of men with melasma are the same as that of women. The main risk factors for melasma affecting men of Indian and Latin origin are sun exposure and fieldwork.[10]

Several endogenous and exogenous factors contribute to the pathogenesis of PIH based on the cause and intensity of inflammation.[17] This condition mainly occurs via epidermal hypermelanosis and the action of dermal macrophages to a varying extent. In PIH, there is an increased melanin formation and/or keratinocyte transfer. Arachidonic acid mediates melanogenesis via oxidative products.[17] Other mediators from keratinocyte release include histamine, fibroblast growth factor, stem cell factor, and endothelin-1. When the skin heals from acute inflammation, it tends to get hyperpigmented or hypopigmented.[9] Maturational dyschromia is mostly seen in black women due to chronic sun exposure.[9] FAN occurs due to increased dermal melanin and the presence of large melanocytes in the epidermis. Another cause is the involvement of pigment epithelium-derived factor (PEDF).[14] Other hyperpigmentation causes include surgical excision of tumor in malignancy[18] and use of tamoxifen for breast cancer[19], vitamin A and B_{12} deficiencies, and epilation induced skin pigmentation.[20,21]

Steroid misuse is a major concern in recent times. Steroid-containing creams are readily available in the pharmacy without a prescription and even post-dated prescriptions are used indiscriminately.[22] Skin-depigmenting agents with steroids without proper physician advice can lead to adverse complications. Skin-brightening topical agents are used by both dark and fair-skinned people. Advertisement of topicals such as creams containing clobetasol has led to steroid abuse at large and lures vulnerable people into buying such products in the market.[22]

The experts agreed that hyperpigmentation is caused due to several factors mainly genetic predisposition, hormonal factors, UV exposure, pregnancy, use of contraceptives, ethnicity, and use of cosmetics. Women undergoing breast cancer therapy with oral tamoxifen suffer from hyperpigmentation. Cutaneous diseases like allergic dermatitis, psoriasis, seborrhea, trauma, and scarring can lead to hyperpigmentation. Experts also agreed that topical steroid abuse is an important cause of hyperpigmentation due to easy availability in the market.

Epidemiology

Hyperpigmentary disorders are the second most frequent complaint in the age group of 15-30 years and the most common complaint in the age groups of 40-54 years irrespective of gender or skin complexion.[2] Hyperpigmentation is widely found in the Indian population and is of major clinical concern. In India, there is a higher prevalence of melasma in sun-exposed areas at higher altitudes where UV radiation predominantly affects darker skin phenotypes.[3] Melasma is found in all races and ethnicities, especially in 90% women, 10% males, and in Fitzpatrick skin types III and IV.[3,9] In women in the age group of 40-60 years, there are 20-30% cases of melasma.[3] Prevalence of melasma in the general population is 1% and in the high-risk population, it is 9-50%; with an average age of onset ranging 20-30 years.[10] Studies showed gender variations in melasma cases with a female to male ratio of 4:1. In a study, 22.4 % of women stated that pregnancy is a precipitating factor for melasma.[23]

PIH is seen in colored skin of both genders. Individuals with a history of acne-induced hyperpigmentation account for more than 70% of the cases before the age of 35 years in either sex.[3] Actinic lentigines are more common in fair-to-medium tone photoaged skin and its prevalence in India is similar to other Asian countries. One-third of the women above 50 years are affected, and it also affects more than half of the population above 70 years.[3] POH is seen in 50% of Indian women with upper eyelid darkening from moderate to severe dark circles as they age.[3]

The expert consensus opined that women usually have a greater prevalence of skin conditions like melasma, PIH, and polymorphic light eruption (PMLE). The female to male ratio of melasma occurrence observed was 9:1. Centrofacial melasma is more common than mandibular melasma. Hormonal link is also associated with hyperpigmentation with the use of OCPs and in female patients with surgically removed uterus and ovaries. PMLE is seen between the ages of 20-30 years and in females who are dieting and having limited sun exposure. It also occurs in men who work outdoors and in people with a history of autoimmune disorders, vitamin D deficiency, and eczema. Tinea faciei can also lead to PIH.

Diagnosis

Diagnosis is based on findings from the history of prior inflammation as in cases of acne, eczema, psoriasis, viral exanthems, arthropod assault, or trauma.[9] History for hyperpigmentation must include details regarding the onset of disease, gender, residing areas, course of the disease, disease progression, addiction to any substance, occupation history, and family history.[24] Physical examination includes observing small to large hyperpigmented patches of various sizes, the color of the patches, and the examination of the nails and mucosa.[9,24] General investigations include complete blood count, liver function test, monitoring of blood glucose, T3, T4, thyroid stimulating hormone, and serum B12 levels and computed tomography (CT).[24] Melasma may be examined with the help of UVA light, although recent studies do not find it useful.[2] Immunohistochemistry may help detect increased intensity of melanin in both dermis and epidermis.[2] Conditions like LPP, discoid lupus erythematosus, phototoxic dermatitis, erythema dyschromicum perstans, phytophotodermatitis, pigmented contact dermatitis, drug-induced pigmentation, poikiloderma of Civatte, nevus of Ota, Hori's nevi and post PIH are the differential diagnosis for melasma. Tools including dermatoscope, and Wood's lamp are used for examining the patches on the skin.[10,13] Reflectance confocal microscopy (RCM) is a non-invasive procedure that identifies skin color changes at the cellular level.[10] Some conditions can resemble hyperpigmentation in appearance; for instance, round hyperpigmented lesions are seen in tinea versicolor or in the case of solar lentigines, which mimic PIH. In such cases, potassium hydroxide scraping test and biopsy can clarify the diagnosis. A history of preceding inflammatory reactions can help in diagnosing PIH differentially.[2,16] For the diagnosis of FAN, patients are asked to test fasting blood glucose and insulin levels. Homeostatic model of assessment of insulin resistance (HOMA2 IR) is a tool used as a specific marker of insulin resistance in patients with FAN.[17] Maturational dyschromia can be misdiagnosed for melasma, PIH, or acanthosis nigricans; and is often considered as a diagnosis of exclusion.[9] Melasma area and severity index (MASI) score is a validated grading system used to measure facial hyperpigmentation and to quantify the response from treatment in melasma.[10,25] MASI involves both subjective and objective assessment of the patient and is used in clinical trials.[10] Mexametry can estimate melanin content and hemoglobin levels, which correspond to the presence of pigmentation or erythema respectively.[26]

The expert consensus stated that early diagnosis and management are beneficial in stopping the progression of hyperpigmentation. Experts agreed that understanding detailed patient history is useful in finding the underlying cause as well as timing, onset, and duration of symptoms, which in turn helps in diagnosis. Other components of history include the profession, social strata, nutritional status including vitamin deficiencies, thyroid function, specific medication, or directed weight loss in recent past, trauma, or injury. History of swimming and exposure to the sun afterward is another very common cause of hyperpigmentation. Dermatoscopy examination is useful in understanding the best treatment option for the patient. The MASI tool is effective in measuring melasma scores. Experts also opined that some conditions are misdiagnosed as melasma, which leads to failure of treatment, which in turn highlights the need for differential diagnosis. They also opined that medicines like hydroquinone can lead to the formation of exogenous ochronosis, which is characterized by hyperchromia with speckling or reticulation, coarse texture, telangiectasias, and atrophy. LPP presents as multiple macular lesions that extend to other body parts; these lesions are characteristic of LPP and are not seen in EDP and Riehl's melanosis. EDP lesions are apparent on sun-exposed areas, unlike LPP lesions, which are present only on photo-exposed areas. Riehl's melanosis is generally observed on the forehead, temples, and the lateral side of the face. In the diagnosis of LPP, a history of trauma such as minor burn, and history of any drug intake is important. FAN can be differentiated from maturational pigmentation based on serum insulin levels, which are elevated in people with FAN. Diagnosis can be based on the measurement of blood pressure, hemoglobin levels, increased HOMA1 IR levels, impaired oral glucose test, lipid profiles, thyroid function test, serum uric acid levels, and sleep study. The expert panel also added that in the diagnosis of PIH, history and site of involvement are important considerations.

Treatment

Hyperpigmentary disorders can be managed by an array of treatment approaches like photoprotection, superficial or topical agents, and other procedures (Figure 2).[6,9,24] The

goal of treatment is to reduce the build-up of melanocytes, stop the generation of melanosomes, and initiate their degradation.[2] Treatment also involves avoiding suspected allergens.[9] Photoprotection is an important aspect in treating hyperpigmentation, to achieve even skin tone, and should be used as the lesions tend to aggravate on UV exposure or visible light.[2,3] It involves the use of broad-spectrum sunscreen, body covering clothes, and accessories.[3] Sunscreen with more than 30 sun protection factor (SPF) along with photoprotective agents is recommended in melasma and PIH.[2,4] The use of sunscreens and hats is essential while going outside or performing outdoor activities during peak hours.[2] People are more compliant in wearing appropriate clothing.[3]

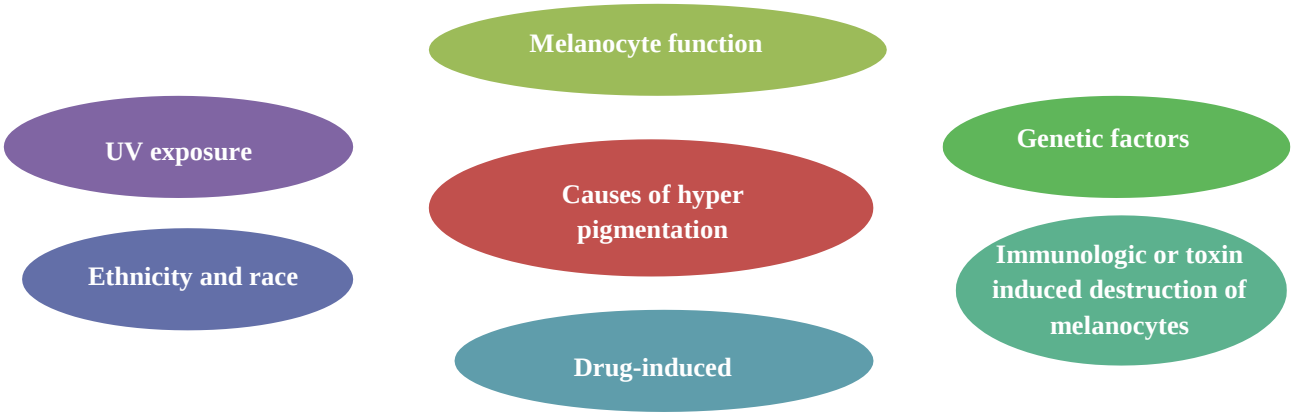

Figure 1: Etiologies of hyperpigmentation.

UV: ultraviolet

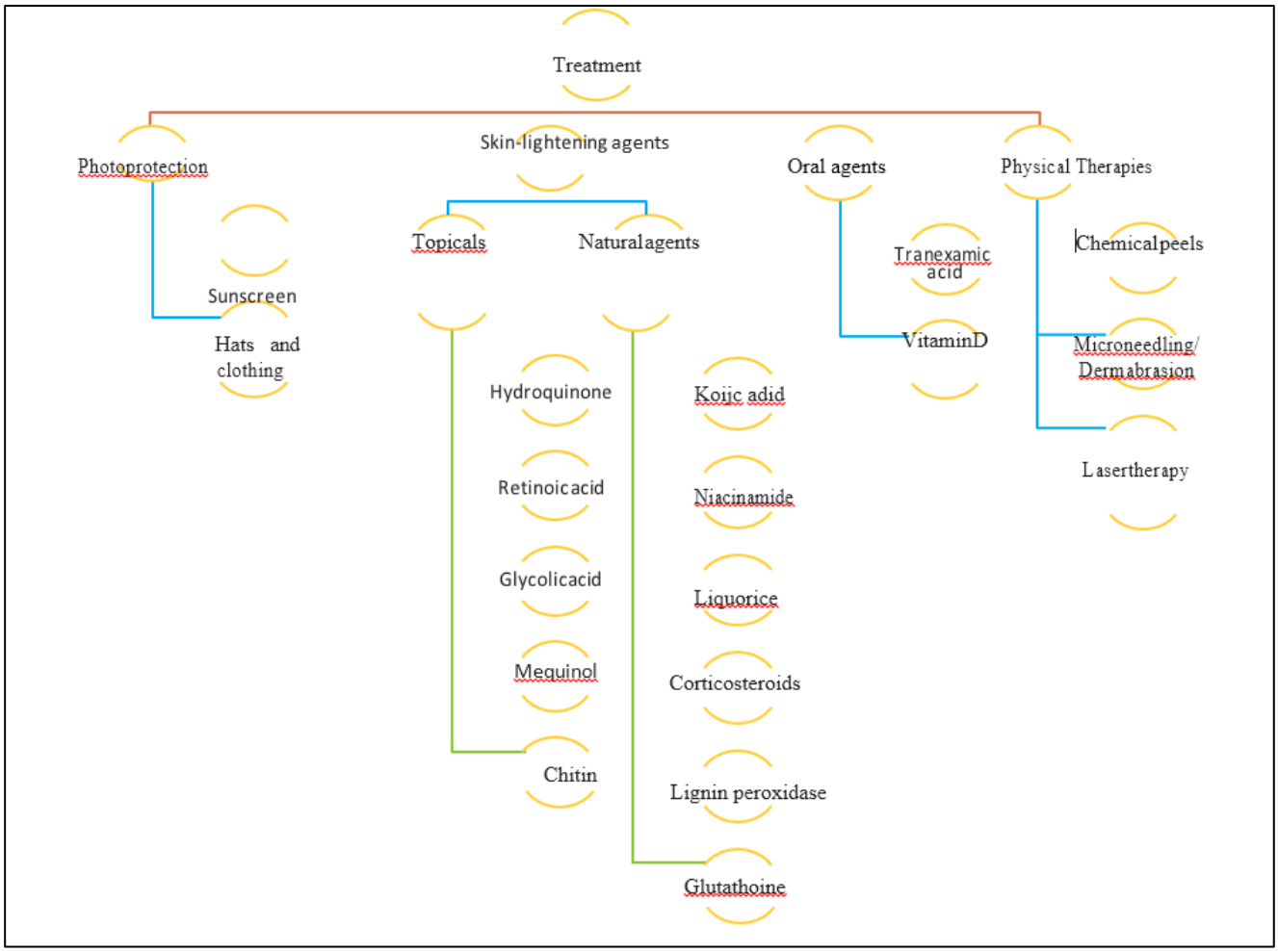

Figure 2: Treatment modalities for hyperpigmentation.

Melasma treatment comprises the use of photoprotective agents, antioxidants, skin lightening agents, exfoliants, and skin-resurfacing techniques.[5,9] It includes the use of topical hydroquinone (HQ) alone or in combination with retinoic acid (RA) or glycolic acid (GA) as a dual combination or as a triple combination along with a topical corticosteroid.[2,5,6,9,10,16] Common side effect of HQ is irritation, but it is safe and effective in treating hyperpigmentation.[16] However, HQ is not recommended during pregnancy due to its higher absorption and possible adverse effects on the foetus, where sunscreen is a safer option.[4] GA and RA alone or in combination with other agents like azelaic acid (AZ), arbutin, kojic acid, and mequinol can be used.[2,5,9,10,16] They are used in combinations due to synergistic actions and have fewer adverse effects.[2]

Table 1 highlights various possible combinations for hyperpigmentation.[27] Retinoids like tretinoin, tazarotene, and adapalene effectively reduce hyperpigmentation when used alone.[16] Moderate to severe cases of melasma may be treated with triple therapy or dual therapy or 20% of AZ may be preferred, which is similar to HQ with fewer adverse effects.[2]

Table 1: Combination therapy for hyperpigmentation.

No.	Skin-lighteners	Possible combinations
1	Hydroquinone	Glycolic acid, retinoic acid, ascorbic acid, vitamin E, corticosteroids
2	Mequinol	Tretinoin, ascorbic acid
3	Tretinoin	Hydroquinone, mequinol, corticosteroids
4	Azelaic acid	Glycolic acid, retinoids, corticosteroids
5	Kojic acid	Glycolic acid, hydroquinone
6	Niacinamide	N-acetyl glucosamine
7	Ascorbic acid	Hydroquinone, mequinol, liquorice extract, soy
8	Liquiritin	Ascorbic acid
9	Soy	Salicylic acid, retinol

For refractory cases, chemical peels or dermabrasion and lasers can be used, but with caution as it may lead to PIH especially for darker skin types.[2,5,9] Women who are on OCPs, if possible, should stop the medicine if there is onset of melasma.[9] Adjuvant therapy includes the use of tranexamic acid (TA), antioxidant vitamins, and plant extracts.[2,10] Oral dose of TA for melasma is 250 mg two times a day and is not recommended for patients with clotting disorders or those with a history of thromboembolism.[5] Side effects such as headache, bloating, tinnitus, menstrual problems, and deep vein thrombosis (DVT) may occur.[10] Methimazole, an oral anti-thyroid medication, causes depigmentation when applied topically.[5] Glutathione is used to reduce inflammation and works as an antioxidant.

For PIH, topical HQ and tretinoin alone or in combination are useful but the treatment time may be little long.[2] Studies showed dramatic improvement with oral isotretinoin in treating acne and PIH.[16] In patients with higher phototypes, peels with glycolic acid or salicylic acid have been found to be beneficial and are well tolerated. Kojic acid, RA, and AZ show varying degrees of effect in PIH.[2,9] Soy extract with retinol and salicylic acid is used for acne-induced PIH.[16] Vitamin D also influences bone health because it is synthesized through skin.[9] Vitamin D supplementation is essential for dark-skinned people or people living in areas with low sun exposure.[9] Vitamin D 1000 IU is recommended by the American academy of dermatology in high-risk patients with severe pigmentation due to sun exposure in pre-existing PIH.[4] Q-switched laser shows variable results in PIH with the risk of hyperpigmentation in dark complexion.[2]

POH can be treated with HQ with results seen after 5-7 weeks, preceded by erythema and desquamation, and its treatment lasts for 3-12 months.[2] The Kligman formulation consisting of HQ, tretinoin, and dexamethasone is usually given in POH, but has adverse reactions associated with it such as erythema, desquamation, irritant, or contact dermatitis.[2] Use of topical RA (0.01-1%) decreases pigmentation by stopping the tyrosinase transcription and thinning the granular layer and epidermis.[2] Its effect is seen after 24 weeks. Side effects include erythema, peeling, burning, and stinging.[2] Other agents used include azelaic acid and kojic acid.[2] Trichloroacetic acid (TCA) peels (15%-25% or higher) applied superficially can treat perioral hyperpigmentation (POH).[2] GA (50-80%) results in epidermolysis when applied topically for a few minutes and then is later washed with water or sodium bicarbonate. Care must be taken and skin must be assessed before the procedure.[2] In the case of excessive pigmentation, q-switched lasers are used with proper care to avoid injury to the eyes.[2,13] In POH secondary to saggy skin and age-related changes, ablative and non-ablative procedures can show results as it involves tissue contraction.[2]

Mequinol is effective in treating solar lentigines.[16] For lentigines sun protection, skin-lighteners, cryotherapy, and laser are other effective options.[9] Laser treatment is beneficial for solar lentigines since it effectively destroys pigmentation.[11] CO_2 lasers are useful but require more time for healing.[11] Nanosecond and picosecond-switched lasers are usually a faster method with the requirement of only one or two treatments. Biophotonic treatment comprising of light-emitting diode (LED) lamp enhances the overall skin appearance.[11]

LPP treatment includes topical steroids, immunomodulatory agents, and skin lighteners.[9] For actinic lichen planus (ALP), topical and intralesional corticosteroids and anti-malarial drugs like hydroxychloroquine, acitretin, and ciclosporin are used.[9]

In acanthosis nigricans, topical and oral retinoids have shown good results.[2] Keratolytic agents like ammonium

lactate 12% or triple combination therapy (4% HQ and 0.05% AR and 0.01% fluocinolone acetonide) can be considered.[2] Oral agents like isotretinoin and procedures like dermabrasion, alexandrite laser, and TCA may be used.[2] Natural agents can be used as alternatives. Table 2 highlights the important natural skin depigmenting agents.[25] Kojic acid is obtained from fungi and is effective in melasma, but comes with the side-effect of irritant or contact dermatitis. Niacinamide, a form of vitamin B3, reduces proinflammatory markers. Other agents include liquorice, chitin and lignin peroxidase, and glutathione.[16]

Antioxidants like ascorbic acid cause less irritation than HQ and can be used as an adjunctive treatment for patients not tolerating HQ.[9,10,16] Liquorice extract used to treat melasma is a skin-lightening agent and has an anti-inflammatory effect.[9,16]

Other skin lightening agents include soy extract, ellagic acid, mulberry extract, arbutin, green tea extracts, aloesin, niacinamide, resveratrol, n-acetylglucosamine, and lignin peroxidase.[16] Adapalene showed improvement in acne and subsequent hyperpigmentation[16]

Table 2. Clinical use of natural depigmenting agents.

No.	Depigmenting agent	Source	Mechanism	Clinical use
1	Kojic acid	Fungi *Acetobacter*, *Aspergillus*, and *Penicillium*[16]	Inhibits tyrosinase enzyme[16]	Melasma, yet to be studied in PIH[16]
2	Niacinamide	Form of vitamin B3[16]	Stops transfer of melanosome to keratinocytes[16]	Solar lentigines, melasma
3	Soy	Soybean legumes	Inhibits melanocyte phagocytosis by blocking action of PAR-2 pathway[16]	Acne-induced PIH
4	Arbutin	Dried leaves bearberry, pear, cranberry, or blueberry[16]	Hydrolyzes to free hydroquinones and stops tyrosinase activity and melanosome maturation[16]	Solar lentigines, melasma
5	Ascorbic acid (vitamin C)	Fruits and vegetables[16]	Deactivates tyrosinase via a copper ion interaction and reduces dopaquinone, a tyrosinase substrate[16]	Melasma, solar lentigines, UV-induced pigmentation
6	Azelaic acid	Fungi *Pityrosporum ovale* rye, wheat, and barley[25]	Interferes with DNA synthesis and inhibits mitochondrial oxidoreductase, preferentially targets abnormal and highly active melanocytes, competitively inhibits tyrosinase, and reduces free radical formation	Melasma and PIH
7	Aloesin	Aloe vera[25]	Inhibits melanogenesis and dose-dependent reductions in melanin content and tyrosinase activity	UVR-induced hyperpigmentation
8	Mulberry	Dried mulberry leaves of *Morus alba*[25]	inhibits tyrosinase activity, melanin formation, melanin transfer, and ROS scavenger[25]	Melasma, UVR-induced hyperpigmentation
9	Liquorice extracts	Root of herb *Glycyrrhiza glabra linneva*[25]	Scavenges ROS, inhibit UVB-induced pigmentation and tyrosinase, and possess anti-inflammatory properties[25]	Melasma, UVR-induced hyperpigmentation
10	Ellagic acid	Trees, nuts, and fruit[25]	inhibits melanogenesis through the reduction in tyrosinase activity[25]	Melasma, hyperpigmentation and dark spots

PAR-2: proteinase activated receptor-2; PIH: post-inflammatory hyperpigmentation; ROS: reactive oxygen species; UVB: ultraviolet-B; UVR: ultraviolet radiation

Cosmetic camouflage involving tinted products are useful in providing heavy coverage for facial hyperpigmentation.[9,27]

Physical therapies

Chemical peels are used either as a single therapy or in combination with other treatments in melasma, especially GA and TCA peels.[10,16] Salicylic acid peels have shown benefit in treating acne and PIH.[16] Irritation is the side effect that may lead to dyspigmentation. It is cost effective and safe for skin pigmentation.[28] Caution should be exercised and deep peels must be avoided to prevent permanent damage.[16]

Microneedling is used to create small channels that deliver minute amounts of medication intradermally.[10] Dermabrasion is used in cases of resistant melasma and has

shown improvement when combined with other topical agents.

Laser therapy is usually the second and third-line treatment approach. Q-switched lasers can be used in patients with nevus of Ota and/or Hori's nevi. Laser therapy should only be used by expert physicians and only if other treatment options do not work. Use of sunscreens is mandatory before and after laser therapy, and also pre-and post-treatment with skin-lightening agents.[16]

Expert opinion on treatment

The expert panel agreed that treatment for hyperpigmentation includes the use of phenolic and non-phenolic agents. Phenolic agents include hydroquinone and mono benzyl ether of hydroquinone and non-phenolic agents like tretinoin, adapalene, topical corticosteroids, azelaic acid, arbutin, kojic acid, and liquorice. Use of sunscreen and moisturizers are required. They agreed that hydroquinone is the gold standard for treating melasma at 2-4% concentration. They also added that kojic acid, arbutin, and 4-n-butyl resorcinol are promising options in depigmentation. The triple combination of 4% hydroquinone, 0.05% retinoic acid, and 0.01% fluocinolone acetonide is recommended for a longer duration of 6-12 weeks for dark patches or in non-responders.

The expert panel emphasized that combination therapy is more effective than monotherapy. Since steroids are widely available in India, treatment with a triple combination needs to be tapered gradually. Broad-range sunscreens with physical and chemical blocking agents are preferred. Gel-based sunscreens for summers and silicon-based sunscreens are more cosmetically appealing. Oral agents like vitamin C, tranexamic acid, and glutathione are used. The tranexamic acid dose of 500 mg is given per day for at least three months after checking the stroke history of the family.

The expert panel also opined that gentle procedures on the skin are preferred over harder ones that provoke hyperpigmentation. They also agreed that lasers are not used as first-line treatment and are used only when other treatments fail. They also opined that cosmeceuticals are used for resistant melasma as they are desirable and give faster results.

The expert panel stated that treatment for LPP starts with oral tretinoin 30 mg once daily for a month, after which it can be tapered to 20 mg once daily and is lowered based on the lightening of the skin. Other agents include tacrolimus applied topically with photoprotection and fractional lasers. Drug-induced LPP can be prevented by avoiding causative drugs like proton pump inhibitors (PPIs), chloroquine, anticonvulsants, and antitubercular drugs. In the case of FAN, along with insulin treatment and weight reduction, topical retinoic acid can be applied.

For POH, the expert panel stated that chemical peels of GA 20% or lactic acid can be used around the eye, only if the patient has a history of diet, sleep, anemia, or sight problems. Hyaluronic acid in combination with under eye creams or kojic acid or hydroquinone 2% is preferred. PIH is managed effectively if it occurs on the face or any exposed area. Topical agents like kojic acid, azelaic acid can be used. Azelaic acid for acne works best along with benzoyl peroxide. Oral PIH is best managed with tranexamic acid.

Triple combinations are not preferred in case of PIH due to acne, which can be treated using arbutin or tretinoin, or salicylic acid peels. Microdermabrasion works well in acne-induced PIH. Oral antioxidants like beta carotene, vitamin C, zinc, and vitamin A are used in combinations. For localized pigmentation as in the case of solar melanosis, kojic acid, arbutin, or a combination of tretinoin and glycolic acid are used.

Adherence to treatment

Patient adherence is low in dermatological conditions that require the use of topical agents, although they are effective in treating hyperpigmentation.[29] The chronicity of pigmentation can lead to non-adherence of intended treatment mainly with sunscreen use.[2]

There are misconceptions that male patients are less concerned than female patients when it comes to appearance and following a strict skincare routine.[30] Men are more motivated to follow prescribed medications in conditions like melasma than females. Some patients may like fragrance-based products, oily texture, or camouflaging agents while some may not. Most of the patients may find it cumbersome to use topicals several times during the day or even a single application. Patient needs, preferences, and expectations must be noted by the physician before prescribing any treatment. Clinicians are required to make tailor-made treatment regimens considering individual patient preferences irrespective of gender.[30]

Patient counseling can help in educating patients about the disease, treatment course, and prevention strategies and also in answering queries.[24] Sun protection is the mainstay for hyperpigmentation and avoiding recurrence. The importance of sunscreens must be emphasized, and patients must be advised to wear hats and clothes that block sun exposure. Patients need to be counseled to apply sunscreens before and after chemical peels during the daytime, and at night moisturizers should be applied.[28] Proper counselling on the use of sunscreen is necessary to get optimum results.[4] It is important before and after treatment to get maximum results.[16]

The expert panel opined that affordability, the complexity of prescription, and treatment duration are important factors for treatment compliance. Counselling and reassurance contribute to patient adherence. They also

agreed that patients should be made aware of their condition and treatment duration. Providing the patient with reading material such as pamphlets and booklets can help in achieving improved outcomes. The patient should also be counselled with respect to the importance of maintenance therapy. Reminder programs can help in improving patient compliance. Experts also agreed that males are more complaint than females once they agree to follow the treatment regimen. Compliance increases only if the patient observes any improvement. The extent and severity of the lesions is the deciding factor for the nature of treatment. The oral treatment approach is preferred only if it shows positive results in the patient. Dosing frequency and tolerability are important for patient compliance. Pigmentation tracking tools like skin hue cards can help patients monitor improvement. Patients should be advised that the skin hue card is only for the pigment and not for the entire face. Telecommunication may be used by patients who cannot come in person for follow-up visits. Images of the lesion can be sent to the doctor via emails for better assessment.

CONCLUSION

There is a vast majority of patients who suffer from hyperpigmentation disorders. Due to the availability of various over-the-counter medications with inadequate evidence on safety and efficacy, patients are often confused in making the correct choice. Proper diagnosis with evidence-based treatment strategies can help in getting promising results. This expert consensus paper has summarized clinicians' perspectives about diagnosis and management of hyperpigmentation of different causes. The expert panel agreed that treatment compliance is an important factor to consider given that patients discontinue treatment if there are no signs of improvement. Experts also supported the use of combination therapy instead of monotherapy. They opined that patient counselling and reassurance are helpful in adherence to treatment strategy. Use of pamphlets, booklets, or tracking tools like skin hue cards can aid in patient compliance.

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