Review on Skin Hyperpigmentation: Etiology, Diagnosis and Treatment

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ABSTRACT:
Hyperpigmentation is a common dermatological condition. Skin color is determined by melanin and other chromophores and is influenced by physical factors (ultraviolet radiation) and other endocrine, autocrine, and paracrine factors. Being the largest organ of the body, any abnormality in skin color can have impact on the patients’ psychosocial impairment of life. In Indian population have verities of hyperpigmentation condition on skin due to multifactorial region; hence, a multipronged approach is needed in such cases. The biggest challenge in such cases is to treat the hyperpigmentation itself; hence, counseling and general treatment (the use of broad-spectrum sunscreen, the avoidance of sun exposure, etc.) play crucial role, and an interdisciplinary approach may be required, especially when the hyperpigmentation is due to a systemic cause. A thorough understanding of the aetiology and management strategies of hyperpigmentation is of importance in caring for those afflicted and also in the development of new therapies.

KEY WORDS: Transdermal Drug delivery, Microneedle, Solid microneedle, Hydrogel micro needle.

INTRODUCTION
Hyperpigmentation is a common dermatologic condition among patients of all skin types. Pigmentation disorders are the third most common among dermatologic disorders and cause significant psychosocial impairment.1 Hyperpigmentation of the skin is a common complaint in populations. The majority of the world’s population is brown-skinned.2 Variability of constitutive pigmentation around the world is well-established, with some skin tones, especially in Asian and Indian subjects. This review mostly focuses on the skin pigmentation and its variation, as well as associated pigmentary disorders among the Indian population.3 There is great diversity in the color of human skin across the globe.4 Pigment formation is highly complex. Melanocytes in cooperation with enzyme tyrosinase are responsible for the production and conversion of dopa to melanin; melanosomes containing pigment are ingested by the keratinocytes, and the melanin is shed with the stratum corneum cells. Melanin production and skin colour are affected not only by keratinocytes5 figure 1.

Figure 1: A Melanocytes and production of Melanosomes

CAUSES
There are numerous causes of hyperpigmentation. and it can be classified in many ways. An etiological classification would simplify the approach to such cases.
Table 1: Etiological classification of Hyperpigmentation

| (A) Endocrinologic | (i) Addison’s disease  
|                   | (ii) Cushing’s syndrome  
|                   | (iii) Nelson syndrome  
|                   | (iv) Pheochromocytoma  
|                   | (v) Carcinoid  
|                   | (vi) Acromegaly  
|                   | vii. Hyperthyroidism  
|                   | viii. Acanthosis nigricans  
|                   | (ix) Diabetes  
| (B) Nutritional | (i) Kwashiorko  
|                   | (ii) Vitamin B12 deficiency  
|                   | (iii) Folic acid deficiency  
|                   | (iv) Niacin deficiency  
|                   | (v) Tryptophan deficiency  
|                   | (vi) Vitamin A deficiency  
| (C) Metabolic | (i) Porphyria cutanea tarda (PCT)  
|                   | (ii) Hemochromatosis  
|                   | (iii) Gaucher’s disease  
|                   | (iv) Niemann–Pick disease  
|                   | (v) Wilson’s disease  
|                   | (vi) Chronic renal failure (CRF)  
| (D) Tumoral | (i) Mycosis fungoides  
| (E) Physical | (i) Ultraviolet radiation  
|                   | (ii) Ionizing radiation  
|                   | (iii) Thermal radiation  
|                   | (iv) Trauma  
| (F) Occupational | (i) Ultraviolet radiation  
|                   | (ii) Ionizing radiation  
|                   | (iii) Thermal radiation  
|                   | (iv) Trauma  
| (G) Occupational | (i) Pigmented contact dermatitis  
|                   | (ii) Metal deposition in skin – silver, mercury, gold, bismuth, chromates, copper, and cadmium  
|                   | (iii) Chemical exposure – arsenic and aromatic hydrocarbons  
| (H) Medications | (i) Clofazimine  
|                   | (ii) Amiodarone  
|                   | (iii) Minocycline  
|                   | (iv) Zidovudine  
|                   | (v) Antimalarial  
|                   | (vi) Bleomycin  
|                   | (vii) Doxorubicin  
|                   | (viii) Chlorpromazine  
|                   | (xi) Cyclophosphamide  
|                   | (x) EGFR inhibitor  
|                   | (xi) Psoralens  
| (I) Deposits – | exogenous ochronosis  
| (J) Autoimmune | systemic sclerosis  
| (K) Infections | (i) Onchocerciasis  
|                   | (ii) HIV-associated hyperpigmentation  
| (L) Miscellaneous | (i) Tattooing  
|                   | (ii) Lichen planus pigmentosus (LPP)  
|                   | (iii) Ashy gray dermatosis  
|                   | (iv) Carbon baby syndrome  
|                   | (v) Bronze baby syndrome  
|                   | (vi) Extensive Mongolian spots  
|                   | (vii) Giant melanosytic nevus  
|                   | (viii) Adrenoleukodystrophy  
|                   | (ix) Familial progressive hyperpigmentation  
|                   | (x) Generalized fixed drug rash  
|                   | (xi) Postinflammatory hyperpigmentation following pemphigus or erythroderma  
|                   | (xii) Idiopathic eruptive macular pigmentation (IEMP)  
|                   | (xiii) POEMS syndrome  
|                   | (xiv) Cronkhite–Canada syndrome  
|                   | (xv) Dyschromatosis universalis hereditaria  
|                   | (xvi) Reticulate acropigmentation of Kitamura  

COMMON HYPERPIGMENTARY DISORDERS

This section includes studies carried out on the variation of Indian skin tones across various geographical locations and their susceptibility to common Hyper-pigmentation disorders. In this study, I focus on hyper-pigmentary disorders such as, important hyper pigmentary disorders in India, namely, melasma, post inflammatory hyperpigmentation (acne, psoriasis, atopic and contact dermatitis, lichen planus, trauma, drugs, and fixed-drug eruptions), periorbital hyperpigmentation, generalized hyperpigmentation, Gingival pigmentation, Solar lentigines, Ephelides (freckles), Café-au-lait, macules, Nevi, Melanoma and precursors.

FEATURES OF HYPERPIGMENTATION

Clinical examination

After taking history, the patient has to be examined. First, a general examination of the patient has to be performed to assess the general health of the patient.
A.  General examination

Altered mental status and clubbing is found in patients with Wilson’s disease. Pallor is a feature in those with chronic renal failure (CRF), Gaucher’s disease, and Niemann–Pick disease, whereas icterus accompanies Wilson’s disease and hemochromatosis. Pedal edema is an important finding in patients with CRF, kwashiorkor, POEMS, and hyperthyroidism. Pulse rate often gives important clues for diagnosis. Tachycardia is found in those with Cushing’s syndrome, pheochromocytoma, carcinoid syndrome, and hyperthyroidism. However, bradycardia is a feature of Addison’s disease. Hypertension is a vital pointer toward Cushing’s syndrome, pheochromocytoma, CRF, systemic sclerosis, etc.¹³

B.  Cutaneous examination

1.  Examination of skin: Different skin condition have different features  
Table 2.

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Distinguishing features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-inflammatory hyperpigmentation¹⁴</td>
<td>History or presence of inflammation with erythema and/or scaling and Epidermal hypermelanosis will appear tan, brown, or dark brown and may take months to years to resolve without treatment.</td>
</tr>
<tr>
<td>Maturational dyschromia¹⁵</td>
<td>Darkening of malar cheeks and forehead in mature richly pigmented skin. polygonal-shaped dark brown to black-colored macular pigmentation over the zygomatic areas of the face. The lesion had ill-defined borders and a rough surface.</td>
</tr>
<tr>
<td>Periorbital hyperpigmentation¹⁶</td>
<td>to detect involvement of the upper or lower or both eyelids and extension beyond the periorbital region, color of hyperpigmented areas (light brown/dark brown/red/blue).</td>
</tr>
<tr>
<td>Riehl melanosis¹⁷</td>
<td>occurs on the face and neck and is characterized by the rapid onset of gray-brown reticular pigmentation. Typically preceded by mild erythema and pruritus, followed by a diffuse-to-reticulated hyperpigmentation.</td>
</tr>
<tr>
<td>Melasma¹⁸</td>
<td>Melasma is characterized by brownish macules with irregular contours and clear limits. It appears in sun-exposed areas, especially the face and cervical region, and, less commonly, in the arms and sternal region.</td>
</tr>
<tr>
<td>Exogenous ochronosis¹⁹</td>
<td>Cutaneous disorder characterized by banana-shaped, yellow-brown deposits in the dermis and blue-black hue in the skin due to the deposition of small ochre-colored pigment in the dermis secondary to prolonged skin lightening agents or unprotected sun exposure.</td>
</tr>
<tr>
<td>Acanthosis nigricans²⁰</td>
<td>Acanthosis nigricans is characterized by dark, coarse, thickened skin with a velvety texture. The earliest change is grey-brown/black pigmentation with dryness and roughness that is palpably thickened and covered by small papillomatous elevations, giving it a velvety texture. As thickening increases, skin lines are further accentuated and the surface becomes mammilated and rugose, with the development of larger warty excrescence and Symmetric, hyperpigmented, velvety plaques on the neck and axillae.</td>
</tr>
<tr>
<td>Dermatosis papulosa nigra²¹</td>
<td>The lesions of DPN initially present in adolescent patients as minute, round, skin-colored to dark brown macules, resembling freckles, gradually becoming papular and increasing in size and number with age.</td>
</tr>
<tr>
<td>Nevus of Ota²²</td>
<td>Extraoral examination revealed the presence of an asymptomatic blue-grey lesion on the face that had been Onset in infancy or puberty. The discoloration gradually progressed to involve the forehead, temple, malar, periorbital area, sclera, lower palpebral, and ala of the nose and with interspersed pinpoint lentigo-like spots.</td>
</tr>
<tr>
<td>Hori naevus²³</td>
<td>Asians, primarily Chinese and Japanese, women aged 20–70 years. The malar region was the most frequently affected area. Blue-grey to grey-brown macules primarily on the zygomatic area and less often on the forehead, temples, upper eyelids, and root and alae of the nose.</td>
</tr>
<tr>
<td>Ephelides²⁴</td>
<td>Red to light brown skin color and 1–3-mm well-demarcated hyperpigmented macules that are round, oval or irregular in shape. Areas affected like, Face, neck, chest, arms.</td>
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</tbody>
</table>
Lentigines\textsuperscript{24,25} Lentigines are characterized by their small size (< 0.5 cm), irregular borders, and discrete markings of different shades of brown and black. Area affected like, Sun-exposed skin, face, hands, forearms, chest back and shins.

Lichen planus pigmentosus\textsuperscript{26} Lichen planus pigmentosus (LPP) is a condition characterized by persistent and asymptomatic slaty-gray pigmentation, predominantly in the face. Oval or irregularly shaped grey-brown to brown macules and patches in sun-exposed areas.

Erythema dyschromicum perstans\textsuperscript{27} A physical examination revealed brownish-grey to greyish-black pigmented macules and patches on the trunk and extremities. Inflammatory phase with rim of erythema. Distribution also includes non-sun exposed areas.

Actinic lichen planus\textsuperscript{28} The eruption was distributed over sun-exposed areas, with particular predilection for the face. In most cases the lesions consisted of erythematous brownish plaques with an annular configuration.

Erythromelanosis follicularis faciei et colli\textsuperscript{29} symmetrical patches of reddish-brown pigmentation with tiny and follicular papules that begin on preauricular areas and cheeks and gradually spread to the submandibular areas. there was diffuse dark-brown reticulated pigmentation and Well-demarcated erythema.

Post-chikungunya pigmentation\textsuperscript{30} Small macules of brown-black pigmentation or slate-like pigmentation of the centrofacial area. History of fever, morbilliform skin eruption and polyarthritis.

2. Examination of the nails: All the finger-nails and toe nails were diffusely pigmented without discrete band appearance. Blackish discoloration spread onto the proximal nail folds from all the nails. No pitting or any history of any inflammation or injury to the nail was recognized.\textsuperscript{31}

3. Examination of the oral mucosa: The color of physiological pigmentation can range from light brown to almost black. They may greatly vary in color as blue, purple, brown, gray or black depending on the quantity and site of melanin in the tissues.\textsuperscript{32}

C. Systemic examination
Systemic examination is more important for diagnosis of hyperpigmentation in many cases, we may come across important findings that help us associate them with the dermatological lesions, for example, hyperpigmentation induced by Grave’s disease\textsuperscript{33}, vitamin B12 deficiency\textsuperscript{34}, hepatomegaly is a feature of hemochromatosis\textsuperscript{35}.

Treatment Options for Hyperpigmentation
Treatment is mostly cause specific, but some general measures such as photoprotection (avoidance of sun exposure and the use of broad-spectrum sunscreens) and the avoidance of known triggers always help. Counseling is an integral part of the therapy, because many conditions are difficult to cure. The management of some the diseases has been summarized in Table 3.

<table>
<thead>
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<th>Table 3: Treatment of conditions causing hyperpigmentation\textsuperscript{36,37,38,39}</th>
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<td>-------------------------------</td>
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<td><strong>Alkaptonuria</strong></td>
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<td><strong>Vitamin B12 deficiency</strong></td>
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CONCLUSION

Hyperpigmentation is common skin disorders that includes different types of disorders on various parts of body. Hyperpigmentation are multifactorial disorders. General examination and systemic survey hold crucial importance when the cause of the pigmentation is an underlying systemic disease. The clinical diagnosis is clear in most of the cases with the help of a proper cutaneous examination with special reference to the site and color of the pigmentation. Besides, associated cutaneous findings and an examination of the Oral mucosa, and nails give important diagnostic clues. Depending on the differential diagnoses, relevant blood investigations. The treatment of the presentation is mainly directed toward photoprotection, topical steroids, calcineurin inhibitors, systemic agents, deficiency of vitamin B12, niacin and the management of the underlying disease.

REFERENCES