FEATURE ARTICLE

The Top 10 Things You Need to Know About Acquired Pigmentation Disorders

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ABSTRACT: Disorders of pigmentation can be acquired or inherited. The acquired disorders present an opportunity for surveillance and treatment to prevent morbidity and improve quality of life. In this article, we delineate the acquired causes, pathogenesis, and treatment options of disorders of skin hyperpigmentation or hypopigmentation.

Key words: Acquired Pigmentation Disorders, Dyspigmentation, Hyperpigmentation, Pityriasis alba, Vitiligo

Melanin, a brown or black pigment, determines the color of skin and hair. This pigment is formed in melanocytes from tyrosine (Hurwitz, 2006). Melanocytes are cells derived from the neural crest that migrate to the basal layer of the epidermis during embryogenesis and become dendritic secretory cells when mature. Abnormal skin hyperpigmentation or hypopigmentation results from aberrant melanin production, melanosome transport, or melanocyte development.

Defects in the melanin production pathway can be inherited or acquired. The genodermatoses related to disorders of pigmentation are described in a separate article (Chow & Jacob, 2015). Here, we describe the “top 10 things to know about” the disorders of hyperpigmentation and hypopigmentation caused by functional abnormalities secondary to an acquired extrinsic or intrinsic cause.

1. Acquired Versus Inherited Pigmentary Disorders

Acquired disorders are medical conditions that develop over the course of an individual’s life. In contrast, an inherited pigmentary disorder arises secondarily to genes passed on from parents to their offspring. Thus, an acquired pigmentary disorder is hypopigmentation or hyperpigmentation that is not present at birth and is not secondary to an inherited genetic defect from the parents. Examples of such disorders include vitiligo, melasma, and postinflammatory pigment alterations secondary to tinea versicolor, among others. In contrast, inherited pigmentary disorders are secondary to a genetic aberrancy and can include such syndromes as tuberous sclerosis, neurofibromatosis, and the Carney complex.

2. Pathophysiology

Human skin color is primarily determined by the type, quantity, and distribution of melanin pigment in the skin, which is regulated by a complex array of genetic, environmental, and endocrine factors (Costin & Hearing, 2007). Aside from determining skin color, melanin also protects the skin against ultraviolet (UV) radiation. Extrinsic and intrinsic disturbances in the physiologic and biological processes that affect the production and transport of melanin, such as UV light, certain medications, and the hormonal changes that occur during pregnancy, can also affect skin color.

Melanocytes are the secretory cells that produce melanin. The quantity of melanocytes in human skin across ethnicities is constant within each individual; however, skin color is determined by the size, number, and distribution of melanosomes within keratinocytes (Haake & Holbrook, 1999). Melanocytes reside in the basal layer of the epidermis. After the production of melanin, the melanocytes transfer...
the pigment to surrounding keratinocytes through melanosomes, which are specialized membrane-bound organelles (Costin & Hearing, 2007).

The synthesis and distribution of melanin depends on several steps. First, melanoblasts (melanocyte precursor cells) must develop and migrate from the neural crest to their final peripheral sites. Second, the melanoblasts must differentiate into melanocytes after migration. Finally, the melanocytes must then proliferate and begin producing melanosomes, which must undergo a maturation process. Three enzymes are required to synthesize melanin within these organelles, including tyrosinase, dopachrome tautomerase, and tyrosinase-related protein 1 (Haake & Holbrook, 1999).

Melanosomes can produce several types of melamins: eumelanin (black-brown), pheomelanin (yellow-red), a combination of eumelanin and pheomelanin termed mixed melamins, and neuromelanin. These pigments differ in their chemical, structural, and physical properties and play disparate molecular roles in different anatomic regions (Hearing, 2000). Once the melanosomes are transferred to neighboring keratinocytes, the epidermal melanin unit becomes a functional entity that can respond through paracrine and autocrine mechanisms to environmental stimuli. Thus, human skin pigmentation is a dynamic process determined by numerous internal and external factors (Hearing, 2000).

### 3. Causes of Human Skin Hypopigmentation or Hyperpigmentation

Internal and external processes that affect the steps in the complex melanin production and transport pathway can potentially lead to abnormalities in skin pigmentation. Internal processes include autoimmune etiologies (e.g., vitiligo) and endocrine dysfunction (e.g., insulin resistance). In contrast, external processes can include medications (e.g., minocycline), sun exposure (e.g., solar lentigo), and post-inflammatory hyperpigmentation responses to injury and infections (e.g., tinea versicolor).

For instance, numerous medications can cause skin discoloration. Heavy metals, such as silver, bismuth, arsenic, and gold, can cause hyperpigmentation through binding and inactivating sulfhydryl compounds that function to inhibit tyrosinase activity. This process results in melanogenesis (Molokhia & Portnoy, 1973). Chemotherapy agents are hypothesized to cause hyperpigmentation through toxic effects on melanocytes, stimulation of melanosomes, and inflammation (Costin & Hearing, 2007). Levodopa, which is used for the treatment of Parkinson’s disease, is hypothesized to enhance melanin biosynthesis through possible extracellular oxidation (Hendrix & Greer, 1992). Other medications that have been associated with skin hyperpigmentation include sulfonamide and tetracycline antibiotics, nonsteroidal anti-inflammatory medications, diuretics, hydantoin antiepileptics, and psychoactive medications (Levantine & Almeyda, 1973). The pathophysiology of common causes of hypopigmentation and hyperpigmentation are described in Tables 1 and 2.

### 4. Epidemiology and Risk Factors

The epidemiology of acquired pigmentation disorders varies widely by disease association. These are described in Tables 1 and 2. Dyspigmentation can affect the young or the older adults and both men and women around the world. These epidemiologic clues can aid in diagnosis. For example, tinea versicolor should be near the top of the differential diagnosis for scaly hypopigmented macules on the chest of a teenaged patient living in a humid environment. In endemic regions, infectious causes must also be ruled out; for example, pinta is a treponemal disease that is similar to syphilis and causes hypopigmentation.

### 5. Prevention

A critical intervention in the prevention of hyperpigmentation is sun protection, as exposure can exacerbate the dark areas through deposition of melanin into the skin. Sun exposure can lead to both acute and chronic pigmented darkening. In the immediate (acute) setting, UV light (specifically UVA and, to a lesser extent, UVB) oxidizes tyrosine in the skin and ultimately forms melanin, causing skin darkening (Joshi, Carraro, & Pathak, 1987). In the chronic setting, hyperpigmentation secondary to UVU/UVB exposure arises from activation and proliferation of the exposed melanosomes (Gilchrest, Blog, & Szabo, 1979).

Furthermore, the cessation of aggravating or inciting exogenous factors should be pursued, and infections should be treated appropriately. Underlying dermatoses, such as acne, must be treated, and allergens and irritants need to be avoided in contact dermatitis to prevent further development of dyspigmented lesions.

### 6. The Social Impact of Dyspigmentation

Patients with dyspigmentation, for example, vitiligo and pigmented contact dermatitis, both of which can affect the face, may have their quality of life significantly affected secondary to the impact that their disease has on appearance. Patients may experience depression, anger, embarrassment, and shame. They may worry that their disease will continue to progress (Sampogna et al., 2008) or be contagious. Facial lesions in particular can be associated with low self-esteem, social withdrawal, and lower school and work productivity. Furthermore, patients who elect to pursue medical treatments and procedures can experience high financial burdens for results that may not reach their expectations (Handel, Miot, & Miot, 2014).

Thus, it is important to discuss the etiology of the dyspigmentation with patients and explore their level of distress involving their disorder. Patients should be reassured of their prognosis but also given realistic expectations regarding the efficacy of their treatments.

### 7. Treatment

Treatment options for hypopigmentation or hyperpigmentation include medical and surgical options. In either
<table>
<thead>
<tr>
<th>Lesion Name</th>
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<th>At-Risk Populations/Epidemiology</th>
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<tr>
<td>Postinflammatory hyperpigmentation</td>
<td>Hyperpigmented, irregularly shaped macules and patches in an area after previous inflammation or injury</td>
<td>More common in darker skin types</td>
<td>The inflammatory response causes arachidonic acid to be released and oxidized into such products as leukotrienes and prostaglandins, which stimulate epidermal melanocytes. This stimulation causes increased production of melanin, which is then transferred to surrounding keratinocytes, resulting in epidermal hypermelanosis. Dermal hyperpigmentation is caused by &quot;pigmentary incontinence,&quot; when pigment is trapped by macrophages in the papillary dermis after inflammation-related damage to the basal cell layer (Cardinali, Kovacs, &amp; Picardo, 2012).</td>
<td>Daily sun protection (SPF &gt; 30), Hydroquinone 2%-12%, Tretinoin cream 0.05% ointment (Retin-A), All-trans retinoic acid aqueous gel 0.1%-0.4% with hydroquinone-lactic acid ointment, Salicylic 0.5%-2% or glycolic acid 10% peels, Azelaic acid 20% cream (Azelex), Tazarotene 0.1% cream, Aloe vera leaf extract, Glabridin microsponge-loaded gel</td>
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| Melasma                           | Tan-to-brown progressive skin hyperpigmentation usually of the face that can occur in malar, centrofacial, and mandibular patterns and less frequently isolated on the forearms | Affects over 5 million people in the United States (Grimes, 1995); Prevalence is 8.8%-40% (Werlinger et al., 2007); More common in women > men, pregnant women (15%-50%), women of childbearing age, family history of melasma, and light-brown skin types (Latinos and Asians) | The factors associated with the development of melasma include genetic disposition, sunlight exposure, and hormonal influence (Hughes, 1987; Ortonne et al., 2009). However, the exact mechanism by which melasma arises remains unclear. | Aggressive sun protection (SPF > 30), and cessation of any exposure to estrogen, Hydroquinone, Tretinoin, adapalene, and azelaic acid, Combination of bleaching agents, for example, Tri-Luma, which is composed of tretinoin 0.05%, hydroquinone 4%, and fluocinolone acetonide 0.01% (Ballia & Graupe, 1991; Dogra, Kaur, & Parsad, 2002; Grimes et al., 2010; Sheih & Pandya, 2011). Chemical peels can help a subset of patients (Rivas & Pandya, 2013; Taylor & Anderson, 1994), Laser therapy (judicious) |

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<td>Solar lentigines</td>
<td>Sharply demarcated hyperpigmented macular lesions that increase in size over time and can appear on the hands, face, neck, and forearms (Ortonne, Pandya, Lui, &amp; Hexsel, 2006)</td>
<td>Patients with history of sun exposure</td>
<td>May be caused by repeated past UV light exposure leading to mutagenesis and increased melanin production; Can also serve as a marker for previous sun burns</td>
<td>Cryotherapy (most common and efficacious)</td>
</tr>
<tr>
<td>Erythema dyschromicum pertans (Ashy dermatoses)</td>
<td>Hyperpigmented blue-gray oval or round patches on the face, trunk, and extremities</td>
<td>Most common in Latin America and Asia; More common in darker skinned individuals, women more commonly than men (Zaynoun, Rubeiz, &amp; Kibbi, 2008)</td>
<td>Hypothesized to be mediated by an immunologic mechanism (Gillbro &amp; Olsson, 2011); May also be caused by chlorothalonil, ammonium nitrate ingestion, x-ray contrast media ingestion, other environmental contaminants, and chronic Hepatitis C infection</td>
<td>Spontaneous remission</td>
</tr>
<tr>
<td>Pigmented contact dermatitis (Rehl melanosis; Serrano, Pujol, Cuadra, Gallo, &amp; Aliaga, 1989)</td>
<td>Brownish gray hyperpigmented patches in a reticular pattern with or without erythematous macules or papules that can be especially prominent on the forehead and temples but can be present on the dorsal hands, forearms, and neck</td>
<td>Usually occurs in young and middle-aged women; epidemiological studies not conducted</td>
<td>Contact allergy, most commonly to cosmetic chemicals</td>
<td>Narrow-band UVB</td>
</tr>
<tr>
<td>Poikiloderma of Civatte</td>
<td>Symmetric red-brown hyperpigmented patches in a reticulate pattern</td>
<td>Middle-aged or elderly fair-skinned women; Epidemiology unknown</td>
<td>Chronic sun exposure and hormonal factors, especially in individuals with genetic susceptibility to solar radiation (Katoulis et al., 1999); Photosensitization by chemicals in cosmetics (Katoulis et al., 2002)</td>
<td>Ablative fractional laser resurfacing</td>
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case, aggressive sun protection (at least SPF 30) is the cornerstone of any therapeutic regimen. In general, the medical treatments available for skin hyperpigmentation include measures to prevent underlying dermatoses causing hyperpigmentation (e.g., acne) and to remove offending agents (e.g., long-term minocycline use). Topical retinoids and bleaching agents have varying efficacy depending on the etiology of the condition leading to the pigment alteration. Although topical hydroquinone (both prescription strength and over the counter) has become a standard therapy for hyperpigmentation, current evidence supports combination therapy utilizing several modalities. For example, triple combination therapy with fluocinolone acetonide 0.01%, hydroquinone 4%, and tretinoin 0.05% given for 8 weeks has been associated with greater improvement of melasma by standardized measurements compared with hydroquinone standard therapy (Chan et al., 2008; see Tables 1 and 2).

Several laser and surgical treatments are also available for hyperpigmentation. Laser therapies, including pulse dye laser and ablative fractional laser resurfacing, have shown some efficacy for hyperpigmented patches, particularly for lentigines and postinflammatory hyperpigmentation (Ho et al., 2012; Ong & Bashir, 2012). That said, there may be a significant risk of postlaser pigment alteration, and thus, it is important to first assess for untoward laser effects by performing a test spot in an inconspicuous region, for example, behind the ear. In extreme cases, surgical excision of the dyspigmented region followed by skin grafting might be pursued (Al-Qattan, 2000).

The treatments for hypopigmentation vary based on the mechanism of dyspigmentation and also include medical and surgical treatments. For example, in the autoimmune disorder of vitiligo, ruling out underlying disorders, such as thyroid disease, is necessary. Once this has been done, the patient could opt for treatment with a topical corticosteroid or an immunomodulatory topical calcineurin inhibitor. Infections should be treated with appropriate antifungal or antibacterial therapies. In select cases, phototherapy, excimer laser, and graft surgery may play a role in treatment. Narrow-band light therapy can also be helpful in some cases of acquired hypopigmentation or depigmentation. As a general principle, no singular therapy is completely efficacious, and combination therapies have been shown to yield the best results.

8. Follow-up

Follow-up after the initiation of treatment depends on the proposed regimen and the need for surveillance. In general, patients with dyspigmentation can be reassessed every 3–6 months for evaluation of treatment efficacy and adjustment of the regimen. This also assures that patients are appropriately using their medications and that physicians can withdraw the medications at the earliest sign of adverse event (e.g., exogenous ochronosis secondary to hydroquinone).
# TABLE 2. Hypopigmented Lesions

<table>
<thead>
<tr>
<th>Lesion Name</th>
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<th>At-Risk Populations/Epidemiology</th>
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<th>Treatment Options</th>
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<tr>
<td>Vitiligo (Taieb et al., 2013)</td>
<td>Hypopigmented or milk-white sharply demarcated macules and patches that enlarge centrifugally over time; can be localized, generalized, or universal</td>
<td>Individuals with other autoimmune disease, such as Graves’ disease, Addison, diabetes mellitus, alopecia areata, pernicious anemia, inflammatory bowel disease, and psoriasis. Relative rate of 1%-2%. Thirty percent of cases will have family history of vitiligo (Ortonne, 2008).</td>
<td>Etiology is multifactorial. Leading theories include autoimmune or cytotoxic destruction of melanocytes and intrinsic melanocyte defects. Oxidative stress and neural injury may play a role in some subtypes of vitiligo.</td>
<td>Topical corticosteroids Pimecrolimus and tacrolimus Phototherapy Excimer laser Graft surgery</td>
</tr>
<tr>
<td>Pityriasis alba (Lin &amp; Janniger, 2005)</td>
<td>Multiple symmetric, poorly defined macules and patches with pityriasiform scaling over the face</td>
<td>Children under 16 years old; Prevalence in children of 5% (Kim &amp; Lockey, 2010)</td>
<td>Reduction in active melanocytes and decreased melanosomes and melanosome size in affected skin</td>
<td>Emollients Low-potency topical corticosteroids for erythema or pruritus Excimer laser (Al-Mutairi &amp; Hadad, 2012; Gambichler et al., 2007; Rigopoulos et al., 2006) Topical calcineurin inhibitors Topical selenium sulfide Topical ciclopirox Topical antifungal medications Topical sodium sulfacetamide Oral fluconazole oritraconazole</td>
</tr>
<tr>
<td>Tinea versicolor (Crespo-Erchiga &amp; Florencio, 2006)</td>
<td>Hypopigmented (can also be hyperpigmented) macules and patches on the back or chest</td>
<td>Residents of humid and hot climates, most common ages of 15–24 years; Prevalence of 2%-8% in the national population (Nenoff, Krüger, Ginter-Hanselmayer, &amp; Tietz, 2014)</td>
<td>Infection by Malassezia globosa and Malassezia furfur in the stratum corneum. Genetic predisposition, immunosuppression, Cushing disease, malnutrition, and warm, humid environments</td>
<td>Topical selenium sulfide Topical ciclopirox Topical antifungal medications Topical sodium sulfacetamide Oral fluconazole oritraconazole</td>
</tr>
<tr>
<td>Postinflammatory hypopigmentation (Nicolaidou &amp; Katsambas, 2014)</td>
<td>Hypopigmented macules and patches in an area of previous injury or inflammation</td>
<td>Patients with atopic dermatitis, psoriasis, seborheic dermatitis, sarcoidosis, lupus, or mycoses fungoides</td>
<td>Effect of inflammation and injury on the melanin production and transportation pathway</td>
<td>Spontaneous resolution UVB phototherapy/ excimer laser Epidermal or melanocyte grafting For paucibacillary leprosy, dapson 100 mg self-administered daily plus rifampicin 600 mg monthly supervised for 6–12 months</td>
</tr>
<tr>
<td>Hansen’s Disease (Leprosy; Britton &amp; Lockwood, 2004; Ustianowski &amp; Lockwood, 2003)</td>
<td>Painless, insensate, and possibly hypopigmented patch</td>
<td>Travelers to or individuals from endemic tropical regions; In the United States, 200–300 cases of leprosy reported each year particularly in states with large immigrant populations; also endemic in Texas, Louisiana, and Hawaii</td>
<td>Infection with M. leprae</td>
<td>For paucibacillary leprosy, dapson 100 mg self-administered daily plus rifampicin 600 mg monthly supervised for 6–12 months</td>
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9. The Challenges
An important point to address in the treatment of dyspigmentation is that no single treatment is 100% effective. Combination therapies, both surgical and medical, often yield the best results. Furthermore, the treatments themselves may lead to hypopigmentation or depigmentation at previous lesions, and the treatment of hypopigmentation can lead to hyperpigmentation at previous lesions. For example, hydroquinone has been reported as a cause of secondary hyperpigmentation (exogenous ochronosis) when used for extended periods. Fortunately, this side effect is extremely rare (Makino et al., 2013).

Another important issue to consider is the ethics involving treatments for dyspigmentation (Baumann, 2012), as many dermatology practices now are selling products for skin lightening. This issue has been hotly debated among dermatologists for decades and continues to be a topic for discussion. The American Academy of Dermatology position statement on in-office dispensing includes only prescribing medications in the best interest of the patients in an evidence-based manner (American Academy of Dermatology, 1999). It has been suggested that guidelines delineating an objective, organized approach for therapy be created to lead practitioners and their patients in treatment.

Recently, cosmetic products used to treat dyspigmentation have been a cause for concern. In the United States, it is illegal to use mercury as an ingredient in skin bleaching products. However, skin-lightening products from other countries have been noted to contain this potentially hazardous substance (Boonchai, Desomchoke, & Iamtharachai, 2011; Cristaudo et al., 2013). Mercury is an efficacious active ingredient because it competes with copper in the tyrosinase-regulated step of the melanin synthesis pathway, thereby decreasing pigment production (Vazirnia & Jacob, 2014). However, the metal is an emerging cause of skin hypersensitivity (Forte, Petrucci, & Bocca, 2008) and an increasingly prevalent cause of metal-induced allergic contact dermatitis. Thus, it is important to warn patients about the potential risks of sensitization when using cosmetic products from outside the United States for dyspigmentation.

10. On the Horizon
The treatment of dyspigmentation is an active field of study, with exciting new and emerging clinical studies identifying more and more efficacious treatment modalities for this potentially morbid condition. Moreover, because patients with ethnic skin may experience increased morbidity from dyspigmentation, ongoing research on treatments specifically for this population are extremely important (Alexis, 2013).

Recent data suggest that retinoids and azelaic acid are highly efficacious for treatment of both acne and post-inflammatory hyperpigmentation (Woolery-Lloyd, Keri, & Doig, 2013). Other newly developed formulations have also shown efficacy for treating hyperpigmentation. A 12-week randomized, double-blinded, half-face study revealed greater patient satisfaction and improvement in hyperpigmentation in subjects receiving a brightener formulation containing SMA-432 (a prostaglandin E2 inhibitor) over 4% hydroquinone. Encouragingly, 95% of subjects reported improvement in overall skin condition at the end of the study (Makino et al., 2013). Other medical treatments on the horizon for hyperpigmentation treatment include topical methimazole.
(peroxidase inhibitor), 4-n-butylresorcinol (tyrosinase inhibitor), zinc, arbutin (Makino et al., 2013), soy protein, N-acetyl glucosamine, kojic acid, aloeins, licorice extract, and ascorbic acid (Draelos, 2007).

The use of laser treatment in combination with medical therapies for hyperpigmentation is also an active field of research, although the efficacy of this treatment has been variable (Arora, Sarkar, Garg, & Arya, 2012; Vashi & Kundu, 2013). Recently, a study examining the efficacy of low-fluence Q-switched Nd:YAG laser treatment immediately after microdermabrasion in combination with hydroquinone and tretinoin or vitamin C showed >50% clearance of melasma after 1 month (Kauvar, 2012). The 1927-nm thulium fiber fractional laser has also been shown to improve melasma histologically in a split-face study of 25 patients (Lee, Haw, Kim, Chang, & Lee, 2013). Other studies, however, have yielded mixed conclusions (for a review, please see Arora et al., 2012). Despite these results, the interpretation of our current studies is limited by the short duration of follow-up, and longer-term studies are needed to assess long-term treatment efficacy and adverse effects. It is our experience that melasma often recurs or may even be exacerbated after laser treatment, and thus, caution must be exercised when considering these treatments. New therapies like these continue to emerge, allowing dermatologic providers a wider range of management options for hyperpigmentation.

The emerging therapies for hypopigmentation are mainly focused on vitiligo, given that we have efficacious treatments for the infectious causes of hypopigmentation. Recently, the HI-Light trial showed that lightweight handheld NB-UVB units for the treatment of vitiligo were associated with good treatment adherence and repigmentation rates (Eleftheriadou et al., 2014). Among the surgical methods for vitiligo treatment, split-thickness skin grafts had the highest repigmentation success rates over punch/mini-graft, cultured and noncultured cellular transplantation, and blister roof grafting (Mulekar & Isedeh, 2013). These approaches are among those being investigated, although standardized head-to-head trials for the varied treatment methods are needed (Eleftheriadou, 2013).

SUMMARY

In summary, the acquired pigmentary disorders are a heterogeneous set of conditions that can cause severe distress and quality-of-life issues. In contrast to the inherited pigmentary disorders, these conditions present an opportunity for prevention and early intervention. The treatment of dyspigmentation remains an art and must be individually tailored to each patient. Our understanding about the pathophysiology of each disorder continues to improve, but long-term studies on treatment efficacy and adverse effects are needed to test the many proposed therapies.

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