Vitiligo: A review of the published work

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ABSTRACT
Vitiligo is a common depigmenting skin disorder, characterized by acquired, idiopathic, progressive, circumscribed hypomelanosis of the skin and hair, with total absence of melanocytes microscopically. It occurs worldwide, with an incidence rate of between 0.1% and 2%. Vitiligo is an important skin disease having a major impact on the quality of life of the patient suffering from it. The causes of this condition are uncertain but seem to be dependent on the interaction of genetic, immunological and neurological factors. Vitiligo coexists with other autoimmune disorders, Sutton or halo nevus, and malignant melanoma. The substantial disfigurement associated with vitiligo can cause serious emotional stress for the patient, which necessitates treatment. Because its pathogenesis is still not understood, there is a plethora of different treatments. Among them, topical steroids and narrowband ultraviolet B monotherapy were the most common as current treatments for localized and generalized vitiligo, respectively. Cosmetic improvement can be achieved by camouflage products and self-tanning dyes. The course of vitiligo is unpredictable, but often progressive. Spontaneous repigmentation may occur in a few people (10–20%), mainly in children, but this tends to be only partial and on sun-exposed areas. In this article, we review vitiligo as a whole, including epidemiology, pathogenesis and etiology, histopathology, clinical manifestations, classification, clinical variants, diagnosis and differential diagnoses, specific investigation, treatment, prognosis, psychosocial view and its association with other disorders.

Key words: association, autoimmunity, pathogenesis, treatment, vitiligo.

INTRODUCTION
Vitiligo affects all races and has a long history. It has been known for thousands of years because of its visual phenotype. It is a common depigmenting skin disorder, characterized by acquired, idiopathic, progressive, circumscribed hypomelanosis of the skin and hair, with total absence of melanocytes microscopically. Vitiligo is a psychologically devastating and frequently recalcitrant skin disorder.

The causes of this condition are uncertain but seem to be dependent on the interaction of genetic, immunological and neurological factors. In general, it shows multifactorial etiology and polygenic inheritance.

Although neither life-threatening nor symptomatic (except that depigmented patches burn easily when exposed to the sun), the effect of vitiligo can be cosmetically and psychologically devastating, resulting in low self-esteem, poor body image and difficulties in sexual relationships.

EPIDEMIOLOGY
Vitiligo is the most prevalent pigmented disorder, occurs worldwide, with an incidence rate of between 0.1% and 2%, irrespective of age, race, ethnic origin or skin color.

The incidence of vitiligo in those with racially pigmented skin is higher, although reliable figures are
The prevalence has been reported as high as 4% in some South Asian, Mexican and US populations. In some studies, a female preponderance has been reported, but the discrepancy has been attributed to a presumed increase in reporting of cosmetic concerns by female patients. Although familial clustering of cases is commonly seen, inheritance occurs in a non-Mendelian pattern. Occasionally, it is reported that vitiligo is determined by an autosomal dominant gene of variable penetrance. It has also been reported in monozygotic twins.

Vitiligo commonly begins in childhood or young adulthood, with peak onset of 10–30 years, but it can develop at any age. Several studies report that 50% of cases appear before the age of 20 years. It is rarely seen in infancy or old age. The incidence decreases with increasing age. Barona found that in patients with unilateral vitiligo, the mean age at onset was 16.3 years (95% confidence interval [CI] = 12–19 years), compared to 24.8 years (95% CI = 22–28 years) in patients with bilateral vitiligo.

One study showed that a high proportion of patients with vitiligo were students or pupils or of a high socio-professional level. Most patients with vitiligo attribute the onset of their disease to specific life events (physical injury, sunburn, emotional injury, illness or pregnancy). With the exception of Koebner phenomena, there is no proof that these factors cause or participate in vitiligo.

Approximately 20% of patients with vitiligo have at least one first-degree relative with vitiligo, and the relative risk for first-degree relatives of vitiligo patients is increased by 7- to 10-fold. Galadari et al. evaluated 65 patients with vitiligo. A positive family history of vitiligo was found in 19% of patients. This was 18%, 30%, and 40% in other studies.

PATHOGENESIS AND ETIOLOGY

Vitiligo is a multifactorial disorder, related to both genetic and non-genetic factors. It is generally agreed that there is an absence of functional melanocytes in vitiligo skin and that this loss of histochemically recognizable melanocytes is the result of destruction.

Due to the observed variation in clinical manifestations of the disease, it seems likely that etiology of vitiligo may differ among patients and is complex. Therefore, several theories on vitiligo etiopathogenesis have been combined to formulate a convergence theory of vitiligo.

Genes certainly play a role in all aspects of vitiligo pathogenesis, even response to environmental triggers, and so genetics really should not be separated out as a distinct phenomenon. Only a few vitiligo susceptibility genes have been identified with reasonable certainty. Currently, there is strong support only for HLA, PTPN22, NALP1 and perhaps CTLA4, all genes associated with autoimmune susceptibility. The frequent association of vitiligo with autoimmune diseases prompted investigations of possible HLA associations in vitiligo. HLA types associated with vitiligo in more than one study include HLA-A2, HLA-DR4, HLA-DR7 and HLA-Cw6. Mutation is another theory stated in pathogenesis of vitiligo.

Anecdotal reports of precipitating events by vitiligo patients may provide some clues that point to heritable biological properties that might make the melanocyte of some people susceptible to environmental triggers or other stressors, possibly resulting in melanocyte death by necrosis, apoptosis or pyroptosis, consequent presentation of tolerogens and loss of immune tolerance, and ultimately autoimmunity directed against melanocytes.

Clinical experience suggests empirically that various factors including in particular localized trauma, stress and autoimmune predisposition may act synergistically to induce the disappearance of melanocytes from the epidermis. Similarly to other common chronic disorders, heritable and environmental factors may associate to trigger and perpetuate melanocyte loss in vitiligo.

On the other hand, accumulation of toxic compounds, altered cellular environment, impaired melanocyte migration and/or proliferation, such as virus, psychological (stress and personality characteristics of patients), neural, autoimmune and autocytoperoxid factors can all contribute to vitiligo.

The autocytoperoxid theory postulates that cytotoxic precursors to melanin synthesis accumulate in
melanocytes, causing cell death.\textsuperscript{10} Sometimes, this process is referred to as the self-destruct theory of Lerner.\textsuperscript{1,34}

Segmental vitiligo frequently occurs in a dermatomal pattern, leading to a neural hypothesis.\textsuperscript{35} This hypothesis proposes that elevated levels of some neurotransmitters and catecholamine degrading enzymes injure melanocytes.\textsuperscript{10}

Vitiligo patients tend to have higher scores for anxiety, depression,\textsuperscript{24,30} adjustment disorders, obsessive symptoms and hypochondria.\textsuperscript{30} Thus, there may be a relationship between stress and the development of vitiligo. Al-Abadei\textit{et al.} indicated that psychological stress increases levels of neuroendocrine hormones, affects the immune system and alters the level of neuropeptides, which may be the initial steps in the pathogenesis of vitiligo.\textsuperscript{40,41}

As a theory, vitiligo is the result of autoimmune loss of melanocytes from the skin and hair.\textsuperscript{7,39,42} Strong evidence in favor of the autoimmune hypothesis has been obtained;\textsuperscript{37,42–44} indeed, autoimmunity is the most popular hypothesis.\textsuperscript{13} One major reason is the coexistence of other autoimmune disorders.\textsuperscript{13,14,19,24,43} In addition, the frequency of autoimmune disease is high in their relatives.\textsuperscript{7,37}

Many patients with generalized vitiligo have serum autoantibodies and circulating autoreactive T cells directed against melanocytes and melanocyte components, and a careful analysis of margins of active generalized vitiligo lesions have repeatedly shown sparse infiltrates of cytotoxic T cells.\textsuperscript{37,45,46} Pichler\textit{et al.}\textsuperscript{43} found an elevated ratio of CD4\textsuperscript{+}/CD8\textsuperscript{+} T cells to be a sign of imbalanced lymphocyte immune response in vitiligo patients, but they did not find evidence for a pathological distribution of B cells in peripheral blood within their patients. In addition, increased levels of soluble interleukin (IL)-2 receptor, IL-6 and IL-8 has been found in vitiligo patients, which further suggests that T-cell activation may be a component in vitiligo pathogenesis.\textsuperscript{10,47} The detection of significantly higher expression of IL-6 and tumor necrosis factor (TNF)-\textgreek{a} in vitiligo skin, compared with healthy skin indicates an imbalance of epidermal cytokines at sites of lesions.\textsuperscript{48}

Focal spongiosis and epidermal mononuclear cell infiltrate was found in 48\% and 80\% of both marginal and vitiliginous skin, respectively, in vitiligo patients. Thus, the authors concluded that vitiligo is an inflammatory disease and the epidermal lymphocytic infiltrate is most likely the primary immunological event.\textsuperscript{49}

The histological and some laboratory data support apoptosis rather than cell necrosis as the mechanism of melanocyte loss.\textsuperscript{5,8,50–53}

Helmy\textit{et al.}\textsuperscript{5} revealed highly significant increase in the percentage of apoptotic peripheral blood mononuclear cells in active vitiligo patients versus stable vitiligo patients or controls.

Oxidant stress may also play an important pathogenic role in vitiligo.\textsuperscript{15} It is suggested that the imbalance in the oxidant–antioxidant system rather than oxidative stress might play such a role in vitiligo. Research at the molecular level has also demonstrated deficiency of antioxidant substances in vitiliginous skin. The free radicals are cytotoxic to melanocytes and inhibit tyrosinase.\textsuperscript{9}

Melanins are colloidal pigments, known to have a high affinity for metal ions; therefore, certain metal ions such as copper, zinc and iron were found in high levels in pigmented tissues involved in melanin synthesis. As melanocyte degeneration was greater in active vitiligo, so there should be decreased zinc and copper in pigment tissues with their defective share in melanin synthesis reflecting their higher serum level. So, high serum zinc and copper levels were the result rather than the cause of the disease.\textsuperscript{5}

A new theory has been proposed integrating most phenomena observed in this disease, emphasizing that depigmentation in vitiligo patches results from a chronic detachment of melanocytes that is proposed to be designated as “melanocytorrhagy”, which is possibly related to increased susceptibility to mechanical and other types of stresses.\textsuperscript{24,39,54}

The expression of 1,25-dihydroxy-vitamin D3 receptor has been reported in human melanocytes. Defective calcium uptake is reported in vitiliginous keratinocytes and melanocytes and related to high thioredoxin levels, which could inhibit melanogenesis through downregulation of tyrosinase activity.\textsuperscript{17}

Zinc x-2-glycoprotein (ZAG) is a plasma glycoprotein that was named for its electrophoretic mobility and for its ability to be precipitated by zinc salts.\textsuperscript{55,56} It is a member of the immunoglobulin gene super family and has a 3-D structure that is highly homologous to major histocompatibility complex class I and
II molecules.\textsuperscript{55,57} ZAG regulates melanin production by normal and malignant melanocytes. B-16 recombinant human ZAG tumors have decreased levels of tyrosinase protein and minimal tyrosinase activity.\textsuperscript{55} According to this theory, we proposed that ZAG may interfere with appearing vitiligo patches.

In summary, it is anticipated that the discovery of biological pathways of vitiligo pathogenesis will provide novel therapeutic and prophylactic targets for future approaches to the treatment and prevention of vitiligo and its associated autoimmune diseases.\textsuperscript{6}

**HISTOPATHOLOGY**

A review of the basics of pigment cell biology is followed by a discussion of the characteristics of several disorders of hypopigmentation.\textsuperscript{58}

Histopathologically, the most prominent feature in vitiligo is the alteration of melanocytes at the dermal-epidermal junction.\textsuperscript{59,60} It shows loss of melanocytes and melanin in the white patches, and inconstant lymphonuclear infiltrate in the advancing margins of lesions.\textsuperscript{17,61}

The peripheries of expanding lesions, which are hypopigmented rather than completely depigmented, still show a few dopa-positive melanocytes and some melanin granules in the basal layer.\textsuperscript{59,60}

In the outer border of patches of vitiligo, melanocytes are often prominent and demonstrate long dendritic processes filled with melanin granules.\textsuperscript{59,62,63}

Early lesions show a superficial perivascular and occasionally lichenoid mononuclear at the border. Focal areas of vacuolar change at the dermal-epidermal junction in association with a mild mononuclear cell infiltrate have been seen in the normal-appearing skin adjacent to vitiliginous areas.\textsuperscript{59,62,63} In long-standing lesions, degenerative changes in cutaneous nerves and adnexal structures have been reported.\textsuperscript{59,64}

Specific staining such as the Masson–Fontana method for melanin or dihydroxyphenyl alanine technique for tyrosinase generally show absence of melanocytes from vitiligo lesions.\textsuperscript{17,65} In addition, specific autoantibodies for melanocytic lineage give no evidence of melanocytes in completely vitiliginous skin.\textsuperscript{17,66,67} Accordingly, these histological data are also supported by electron microscopy, which fails to identify melanocytic cells in vitiligo achromic patches. The melanocytes are degenerated and appear to be replaced by Langerhans cells\textsuperscript{1,17,65,68} and in the epidermis of areas around the margins of vitiligo are abnormalities of keratinocytes.\textsuperscript{1}

**CLINICAL MANIFESTATIONS**

Vitiligo is a hypopigmentation disorder where the loss of functioning melanocytes causes the appearance of white patches on the skin.\textsuperscript{12,20} Patients with vitiligo present with one to several amelanotic macules that appear chalk- or milk-white in color,\textsuperscript{15} surrounded by a normal or a hyperpigmented border.\textsuperscript{24} Very rarely, the patches may have a red, inflammatory border.\textsuperscript{24} The lesions are usually well-demarcated, but the margins may be scalloped.\textsuperscript{15}

The patches are of various sizes and configurations. Involvement is symmetrical. The hairs in the vitiliginous areas usually become white also.\textsuperscript{24} Vitiligo lesions are specially marked in dark-skinned individuals.\textsuperscript{1,4,11,17,18,39,69}

Lesions enlarge centrifugally at an unpredictable rate and can appear on any body site, including mucous membranes.\textsuperscript{15} However, initial lesions occur most frequently on the hands, forearms, feet and face.\textsuperscript{15,25} The most commonly affected sites are the face, upper part of the chest, dorsal aspect of the hands, axillae and groin. There is a tendency for the skin around orifices to be affected, namely the eyes, nose, mouth, ears, nipples, umbilicus, penis, vulva and anus. Lesions also appear at areas of trauma, so vitiligo favors the elbows and knees.\textsuperscript{24}

Local loss of pigment may occur around nevi and melanomas, the so-called halo phenomenon. Halo nevi are also common in patients with vitiligo. Vitiligo-like leukoderma occurs in approximately 1\% of melanoma patients.\textsuperscript{24}

Lesions of vitiligo are hypersensitive to ultraviolet (UV) light and burn readily when exposed to the sun.\textsuperscript{17,18,24} It is not unusual to note the onset of vitiligo after severe sunburn.\textsuperscript{24}

Although ocular abnormalities are increased in patients with vitiligo, including iritis\textsuperscript{19,24} and retinal pigmentary abnormalities,\textsuperscript{24} patients have no visual complaints.\textsuperscript{24} Eight percent of patients with idiopathic uveitis have vitiligo or poliosis.\textsuperscript{24}
Vitiligo is currently classified into two major subtypes: segmental vitiligo (type B) and non-segmental vitiligo (type A).\textsuperscript{35,39,69,70} Type B is more rare, includes focal lesions and those restricted to a segment of the integument. It has a dermatomal distribution; after a rapid onset and evolution, it usually exhibits a stable course. Type A is more common, has a potential lifelong evolution, and is associated with Koebner phenomenon and frequently with autoimmune disease.\textsuperscript{17}

From another point of view, vitiligo is classified as segmental, acrofacial, generalized and universal, or by pattern of involvement as focal, mixed and mucosal types.\textsuperscript{15} The generalized pattern is most common.\textsuperscript{24} Another clinical classification, based on the distribution and extension of lesions according to Nordlund, is described in Table 1.\textsuperscript{17,71}

### TABLE 1. Clinical classification of vitiligo according to Nordlund\textsuperscript{17,71}

<table>
<thead>
<tr>
<th>Localized</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal</td>
<td>One or more macules with casual distribution</td>
</tr>
<tr>
<td>Unilateral</td>
<td>One or more macules are localized in a unilateral body region, with a dermatomeric distribution: a typical feature is an abrupt stop of the lesions at the midline</td>
</tr>
<tr>
<td>Mucosai</td>
<td>Unique involvement of mucous membranes</td>
</tr>
<tr>
<td>Generalized</td>
<td></td>
</tr>
<tr>
<td>Vulgaris</td>
<td>Presence of scattered stains extensively disseminated</td>
</tr>
<tr>
<td>Acrofacialis</td>
<td>Patches are localized on distal extremities and face</td>
</tr>
<tr>
<td>Mixed</td>
<td>Coexistence of acrofacialis and vulgaris forms</td>
</tr>
<tr>
<td>Universalis</td>
<td>Depigmented lesions completely or almost completely cover the skin surface</td>
</tr>
</tbody>
</table>

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### CLINICAL VARIANTS

Trichrome vitiligo is characterized by both depigmented and hypopigmented macules in addition to normally pigmented skin. The natural evolution of the hypopigmented areas is progression to full depigmentation. Quadrichrome vitiligo refers to the additional presence of marginal or perifollicular hyperpigmentation. This variant is recognized more frequently in darker skin types, particularly in areas of repigmentation. Cases of pentachrome vitiligo have also been reported with additional blue-gray hyperpigmented macules, representing areas of melanin incontinence (dermal melanin). Occasionally, patients with vitiligo may present with an unusual variant called the confetti type or vitiligo puncte. These patients have several tiny, discrete hypomelanotic macules. Inflammatory vitiligo is characterized clinically by erythema at the margins of vitiligo macules.\textsuperscript{15}

### DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Diagnostic criteria are mainly clinical, based on the findings of acquired, well-demarcated white lesions on the skin, with no associated inflammation that tend to enlarge centrifugally.\textsuperscript{17} Vitiligo lesions are accentuated on Wood's lamp examination.\textsuperscript{15}

Among acquired disorders, post-inflammatory hypopigmentation, chemical leukoderma,\textsuperscript{1,15} tinea versicolor, pityriasis alba, lichen sclerosus et atrophicus,\textsuperscript{1,15,24} morphea,\textsuperscript{24} sarcoidosis,\textsuperscript{15} leprosy\textsuperscript{1} and tertiary stage of pinta\textsuperscript{24} are included in the list of differential diagnoses of vitiligo. In addition, nevus depigmentosus, hypomelanotic macules of tuberous sclerosis, piebaldism, Vogt–Koyanagi syndrome, Waardenburg’s syndrome and Ziprkowski–Margolis syndrome are rare congenital disorders and syndromes in this list.

Morphea and lichen sclerosus et atrophicus are associated with changes in the skin texture.\textsuperscript{1,24} Pityriasis alba has a fine scale, is slightly popular and poorly defined. Tinea versicolor favors the center back and chest, has a fine scale, and yeast and hyphal forms are demonstrable with potassium hydroxide (KOH) examination.\textsuperscript{24} In addition, these areas often fluoresce a golden yellow when examined under a Wood’s lamp.\textsuperscript{1}

In piebaldism, the lesions are present at birth, are usually confined to the head and trunk, and rarely show a hyperpigmented border. Nevus depigmentosus is a circumscribed area of depigmentation, usually present at birth and changing little thereafter. A functional defect in melanocytes, with morphological abnormalities of melanosomes, has been identified.\textsuperscript{1}

### ASSOCIATIONS

Vitiligo coexists with other autoimmune disorders,\textsuperscript{3,13,14,19,24,43} including in autoimmune thyroid
disease, particularly Hashimoto thyroiditis and Graves disease, pernicious anemia, systemic lupus erythematosus, lichen sclerosus, morphea, scleroderma, diabetes mellitus, adrenal insufficiency (Addison’s disease), alopecia areata, hypoparathyroidism, myasthenia gravis, gonadal failure, inflammatory bowel disease, rheumatoid arthritis, psoriasis, autoimmune polyglandular syndrome, Sutton or halo nevus and malignant melanoma. In one study, the prevalence of four autoimmune diseases – namely, rheumatoid arthritis, chronic urticaria, alopecia and psoriasis – were significantly elevated in generalized vitiligo probands and their first-degree relatives. In addition, the prevalence of asthma and diabetes were also higher in familial vitiligo probands.

The significance of some of these associations is debated, perhaps because of the low frequencies.

**SPECIFIC INVESTIGATION**

Associated autoimmune disease should be looked for. Recommended blood tests include thyroid studies, antinuclear antibodies (ANA) and screening for other organ-specific autoantibodies, fasting blood glucose levels and complete blood count with indices for pernicious anemia.

**TREATMENT**

The substantial disfigurement associated with vitiligo can cause serious emotional stress for the patient, which necessitates treatment. Although it is relatively resistant to most of the treatments, spontaneous repigmentation occurs in more than 1–25% of cases. Some studies stated occurrence of repigmentation in 10–20% of patients.

Sun protection of the vitiliginous areas with sunblocks is important, which help prevent sunburn and thus may lessen photodamage as well as the chance that a Koebner phenomenon will occur. Sunscreens also decrease tanning of the uninvolved skin and therefore lessen the contrast with vitiliginous lesions.

Few studies have paid attention to the effects of treatment interventions on the psychosocial consequences of vitiligo. Cosmetic improvement can be achieved by camouflage products and self-tanning dyes. Each camouflage product has its own characteristics, and it is difficult to compare them in terms of efficacy. It depends on skin color, skin type and each patient’s preference. To compare with the usual makeup for beauty, camouflage of vitiligo needs some techniques, including a precise cosmetic application procedure. Moreover, each cosmetic has a different application procedure. The camouflage procedure consists of three steps: (i) apply a base cream; (ii) cover with a foundation selected for each patient; and (iii) dry up with a finishing powder. Some brands of camouflage include Covermark (Covermark, Northvale, NJ, USA), Dermablend (Dermablend, Ridgefield, NJ, USA), Dermacolor (Dermacolor, Charles H Fox, London, UK), Keromask (Christy, London, UK), Veil Cover (Thomas Blake Cosmetics, Durham, UK) and PerfectCover (Shiseido, Tokyo, Japan; Perfect-Cover is only available in Japan). The newer self-tanning creams containing dihydroxyacetone are useful for light-skinned and olive complexioned patients with acral lesions.
photochemotherapy (psoralen plus UV-A [PUVA], psoralen with sunlight [PUVASol]), surgical techniques, topical prostaglandin E (PGE2), and combinations of topical therapies and light treatment. Complementary therapies have also been used, the most interesting being ginkgo biloba, and levamisole which have been reported to have immune-modulating properties. Pseudocatalase cream with Dead Sea climatotherapy are also compatible with repigmentation. Topical fluorouracil, topical melagenina I and II, minoxidil, oral L-phenylalanine, homeopathy, ayurvedic medicine, climtologic and balneologic therapies, are alternative therapies for vitiligo.

The use of a combination of a light source and a photoactive chemical (i.e. psoralen or khellin) administered either orally or topically is the most common method used in practice. If patients do not achieve visible repigmentation after 25–30 sessions with a given psoralen, an alternative therapy should be sought. Topical and systemic PUVA therapy may require 100–300 treatment sessions to achieve complete repigmentation. Westerhof et al. reported that 46 patients treated with topical PUVA and 67% of patients treated with the 311-nm UV-B showed repigmentation. Thus, they concluded that narrowband UV-B is as efficient as topical PUVA but with fewer adverse effects.

The major side-effects of photochemotherapy are severe phototoxic reactions and blistering. Hyperpigmentation (darker than normal color) may temporarily develop in unaffected skin around the white patches during treatments, so worsens the appearance of the vitiligo. Other less common side-effects include photoallergic reactions, hyperkeratosis of lesional skin and, rarely, skin malignancies.

Some studies concluded that topical steroids and narrowband UV-B monotherapy were the most common as current treatments for localized and generalized vitiligo, respectively. Results of individual studies using different types of steroids showed that clobetasol propionate was better than PUVAsol and that betamethasone valerate was better than placebo.

Intralesional and oral corticosteroids have been evaluated in trials with limited significance. Vasistha et al. showed that there was no significant difference in intralesional steroid versus water in treatment of vitiligo. Atrophy, telangiectasia, infection and intradermal hemorrhage were some of the side-effects; therefore, this treatment is not recommended. On the presumption of a role for autoimmunity in the etiology of vitiligo, systemic corticosteroids may arrest the progression of vitiligo and lead to repigmentation by suppressing immunity. The sera of actively spreading vitiligo patients who received oral corticosteroid treatment with clinical improvement showed a decrease in complement-mediated cytotoxicity by autoantibodies to melanocytes and a reduced antibody titer to surface antigen of melanocytes. Seiter et al. evaluated the effectiveness of i.v. methylprednisolone (8 mg/kg bodyweight) administered on 3 consecutive days in patients with generalized vitiligo. In their study, 85% of the patients presenting with progressive disease showed cessation of disease progression after the infusion therapy. Repigmentation was observed in 71% of patients with progressive vitiligo. They showed that high-dose glucocorticoid pulse therapy may represent a therapeutic option in patients with generalized progressive vitiligo, and should be further evaluated in a prospective, randomized, clinical trial.

Lepe et al. reported the mean percentages of repigmentation as 49.3% and 41.3% for clobetasol and tacrolimus, respectively. In their study, 90% of patients experienced some repigmentation after 2 months’ treatment. They concluded that tacrolimus is almost as effective as clobetasol and is better for sensitive areas (e.g. eyelids) because, unlike clobetasol, it does not cause skin atrophy. In another study, tacrolimus was effective for childhood vitiligo, especially on the head and neck (89% response rate during 3 months). Sixty-three percent of patients with lesions on the extremities responded.

Calcipotriol plus photochemotherapy also appears very promising but certainly requires further evaluation. Surgical therapies are only suitable for stable or segmental vitiligo. Split-thickness grafting appears to be better than control, suction blister or combined split-thickness/suction grafts.

Cosmetic tattooing is used for localized stable vitiligo, especially of the mucosal type. The most recent effective and approved therapy for vitiligo is the 308-nm excimer laser with or without topical calcineurin antagonists (tacrolimus and
pimecrolimus). In twice weekly treatment with 308-nm excimer laser, repigmentation occurred in 88.5% of the plaques; 27% of the plaques achieved 75% repigmentation.

Patients with extensive disease (>50% body area) who desire permanent matching of skin color but for whom repigmentation is not possible can be depigmented with 20% monobenzyl ether of hydroquinone, two times daily for 9–12 months. For vitiligo universalis, treatment with topical 4-methoxyphenol and the Q-switched (QS) ruby laser has been effective. QS ruby laser can destroy melanosome in melanocytes and keratinocytes by selective photothermolysis.

PROGNOSIS
The plethora of proposed treatments for vitiligo suggests that there are key limitations to the management of this condition. The course of vitiligo is unpredictable but often progressive. In some people the white patches can remain stable for many years but in others they can enlarge in size while new patches appear or disappear in large areas of the skin surface. Spontaneous repigmentation may occur in a few people, mainly in children, but this tends to be only partial and on sun-exposed areas, often occurring in a perifollicular pattern. It is rarely cosmetically acceptable.

The segmental form of vitiligo is treatment resistant, has an earlier onset and is less frequently associated with other autoimmune phenomena. Because of lack of melanin pigment, there is an increased risk of sunburn and a theoretical increased risk of skin cancer within the amelanotic areas, and there is association with ocular abnormalities, especially iritis, uveitis and retinal pigmentary abnormalities.

SIGNIFICANCE OF VITILIGO REGARDING PSYCHOSOCIAL VIEW
Appearance of skin can condition an individual’s self-image, and any pathological alteration can have psychological consequences. Vitiligo is an important skin disease having major impact on the quality of patients’ life. Many vitiligo patients feel distressed and stigmatized by their condition, and in some cultures it results in affected individuals being ostracized.

Sixteen to 35% of patients with vitiligo experience significant psychiatric morbidity. Depression (10%), dysthymia (7–9%), sleep disturbances (20%), suicidal thoughts (10%), suicidal attempts (3.3%) and anxiety (3.3%) have been found in those affected with vitiligo. Vitiligo can be confused with leprosy, which also causes loss of pigment, thus further stigmatizing patients.

Disease extent and disease severity are strong predictors of the DLQI. Vitiligo on the face, head and neck substantially affects the DLQI, independently of degree of involvement.

Porter et al. studied the effect of vitiligo on sexual relationships and found that embarrassment during sexual relationships was especially frequent for men with vitiligo.

Salzer and Schallreuter reported that 75% found their disfigurement moderately or severely intolerable.

The DLQI questionnaire is a well-known instrument for measuring dermatological distress. Aghaei et al. indicated that mental health in vitiligo patients was poor and it was strongly associated with their quality of life. They showed that there was no relationship of DLQI score with sex. Because the patients with higher DLQI scores responded less favorably to a given therapeutic modality, improving quality of life in this group becomes a very important task.

VITILIGO AND OTHER SYSTEMIC DISORDERS
Association between vitiligo and thyroid disorders
Thyroid functional disorders and autoimmune thyroid diseases have been reported in association with vitiligo and it seems that the incidence of clinical and subclinical thyroid involvement is more common in vitiligo patients than healthy subjects.

It was as early as 1941, when Robert suggested that vitiligo might be connected with an increased activity of the thyroid gland. He noted a distinct rise of the basal metabolism in half of patients tested. In addition, there is also a study reporting a significantly increased prevalence of vitiligo in patients with autoimmune thyroid disease.
compared with patients with non-autoimmune thyroid disease.\textsuperscript{72,107}

The association of autoimmune thyroid disease with \textit{HLA} genes has received much attention and in several populations of different ethnic background an association between the \textit{HLA} system and Graves disease was reported.\textsuperscript{72} Several genes outside the \textit{HLA} system have been found to be associated with autoimmune thyroiditis.\textsuperscript{72,108,109}

Zettinig \textit{et al.} suggest that autoimmune thyroiditis is the most frequent autoimmune disease associated with vitiligo. The chronological order of vitiligo and autoimmune thyroiditis in patients with both diseases is unknown.\textsuperscript{72} But it appears that vitiligo frequently precedes the thyroid involvement; thus, screening vitiligo patients for thyroid function and thyroid antibody seems plausible.\textsuperscript{13} Conversely, Zettinig \textit{et al.}\textsuperscript{72} revealed that in their vitiligo patients, autoimmune thyroiditis presented simultaneously or after the onset of vitiligo.

Hashimoto thyroiditis and Graves disease are the most important and prevalent autoimmune thyroid diseases associated with vitiligo.\textsuperscript{13,110,111}

Various thyroid autoantibodies, including thyroid stimulating antibody, anti-thyroglobulin antibody and anti-thyroid peroxidase antibody, are detectable in autoimmune thyroid diseases, the latter being the most sensitive test for the diagnosis and follow up of this group of diseases.\textsuperscript{13}

Clinical as well as functional abnormalities of the thyroid gland have been reported by many authors to be significantly more frequent in vitiligo patients compared with control groups.\textsuperscript{13,98,112} All but one of the previous studies diagnosed autoimmune thyroid disease only by findings of abnormal thyroid hormones or elevated thyroid antibodies.\textsuperscript{72} Only Hegedüs \textit{et al.} included sonography and a detailed clinical examination in the analysis of their vitiligo patients. He reported a markedly higher frequency (43% in the study group vs 20% in the controls) including also non-autoimmune forms of all sorts of thyroid disease.\textsuperscript{72,105}

Elevated levels of anti-thyroid peroxidase are seen in more than 90% cases of Hashimoto thyroiditis and approximately 75% of Graves disease cases. This figure is only 10% in healthy people although it may reach 30% in the elderly.\textsuperscript{13,110,111} Mandry \textit{et al.} detected anti-microsomal and anti-thyroglobulin antibodies in 50% and 40% of their vitiligo cases, respectively. They showed increased prevalence of organ-specific antibodies in the relatives, as well.\textsuperscript{113}

Morgan \textit{et al.}\textsuperscript{114} also found higher prevalence of thyroid antibodies in vitiligo patients, especially in generalized vitiligo, than healthy people. Dave \textit{et al.},\textsuperscript{115} Grimes, Korkij \textit{et al.}\textsuperscript{116} and Betterle \textit{et al.}\textsuperscript{117} also showed high frequency of anti-thyroid antibodies.

\textbf{Association between vitiligo and other disorders}

An association of vitiligo with other autoimmune diseases was found in 6% of patients.\textsuperscript{32} Moreover, increased risk of autoimmune/endocrine diseases was shown in first- and second-degree relatives of vitiligo patients with positive organ-specific antibodies.\textsuperscript{7,13,112} Compared with controls matched for sex, age and race, vitiligo patients had an increased frequency of clinical autoimmune diseases of the thyroid (7.5%), stomach (0.8%), parathyroid (1%) and adrenal gland (1.3%).\textsuperscript{117}

One study on a Romanian isolated population with a high frequency of familial marriages, showed the existence of one or more autoimmune diseases in 43% of patients with vitiligo. Almost all of the patients with vitiligo and other autoimmune diseases had generalized vitiligo. Among them, 31% had autoimmune thyroid disease, 14% had rheumatoid arthritis and 12% had type 1 diabetes mellitus.\textsuperscript{3}

Zettinig \textit{et al.} showed no statistically significant association between vitiligo and Addison’s disease or diabetes mellitus type 1. They showed that these diseases are much rarer than autoimmune thyroiditis and the number of their cases with these two diseases are far above the reported frequencies in healthy populations.\textsuperscript{72}

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