

Vitiligo: A Comprehensive Review

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Abstract

Background: Vitiligo is a common dermatological condition characterized by the presence of acquired, amelanotic, non-scaly, chalky-white macules with distinct margins on the skin. It is a multifactorial disorder involving the complex interplay of genetic, autoimmune, and environmental factors. Vitiligo can have a significant impact on the quality of life of affected individuals due to its visible nature and the associated psychosocial implications. **Objectives:** This review article aims to provide an overview of vitiligo, including its epidemiology, etiology, clinical features, and current understanding of the underlying mechanisms. The objectives are to explore the prevalence and distribution of vitiligo worldwide, discuss the potential causes and risk factors, and highlight the diverse clinical presentations observed in different subtypes of vitiligo. **Conclusions:** Vitiligo is a complex and heterogeneous disorder with a wide range of clinical manifestations. Although the exact etiology remains elusive, advancements in research have shed light on the involvement of immune dysregulation, oxidative stress, and genetic predisposition in the pathogenesis of vitiligo. Diagnosis of vitiligo is primarily clinical, based on characteristic depigmented macules, while further investigations may be warranted to exclude other conditions. Management of vitiligo involves a multidisciplinary approach, including topical therapies, phototherapy, surgical interventions, and psychological support. While repigmentation outcomes vary, advancements in targeted therapies and immunomodulatory agents hold promise for future treatment strategies.

Keywords: Vitiligo, Epidemiology, Etiology, Clinical Features, Types.

1. Introduction

Vitiligo is a skin condition characterized by the selective loss of melanocytes, resulting in pale patches on the skin. The affected areas display distinctive features, appearing as white macules with clear margins. This depigmenting disorder, which is commonly associated with autoimmune complications, should not be trivialized as merely a cosmetic issue. It can have severe psychological impacts, significantly affecting individuals' daily lives [1].

2. Epidemiology

Vitiligo is a widespread depigmenting skin condition that affects both adults and children worldwide, with an estimated frequency ranging from 0.5% to 2%. It affects individuals of all races, ethnicities, and skin tones, although there are notable geographical variations in incidence rates. For example, China's Shaanxi Province has reported rates as low as 0.093%, while India has reported rates as high as 8.8%. These variations in prevalence may be attributed to cultural stigma, inconsistent reporting, and the visibility of lesions in individuals with darker skin [2].

A comprehensive analysis of prevalence data from over 50 global studies has revealed that vitiligo has a prevalence ranging from 0.06% to 2.28%. The incidence and prevalence of segmental vitiligo, which accounts for 5% to 16% of all cases, are not well understood. Some researchers estimate the prevalence of

segmental vitiligo to be between 5% and 30%. Variability in epidemiological data is due to inconsistent classification of the disease, patient reporting, and demographic differences. While both men and women are equally susceptible to vitiligo, women and girls are more likely to seek treatment due to the social consequences they face [3].

Nonsegmental vitiligo typically emerges between the ages of 10 and 30, but it can develop at any age. Approximately one-quarter of vitiligo patients acquire the condition before the age of 10, and nearly half before the age of 20. Around 70% to 80% develop the disease before the age of 30. Most populations exhibit multiple age-of-onset groups and distinct incidence peaks [4].

3. Pathogenesis

In the complex pathophysiology of vitiligo, melanocytes undergo a loss of functionality. Proposed reasons for the mortality of melanocytes include genetic factors, immune responses, oxidative stress, production of inflammatory mediators, and melanocyte detachment. While the autoimmune nature of vitiligo is widely accepted, the specific involvement of each immune system component in different vitiligo phenotypes is still debated. Various processes, such as immunological attack or cellular degeneration and detachment, may contribute to the progressive loss of melanocytes observed in vitiligo, ultimately leading to

tissue damage. According to the convergence theory, segmental and nonsegmental vitiligo share a similar inflammatory origin. Internal or external damage triggers the production of proinflammatory cytokines and neuropeptides, resulting in vasodilation and an immune response [5].

4. Risk Factors of Vitiligo

The risk factors associated with vitiligo include age below 30 years, with the average onset occurring at around 20 years of age, and in 80% of patients, the first symptoms are encountered before the age of 30. Additionally, having a family history of vitiligo is a risk factor, as up to 20% of patients with vitiligo have at least one first-degree relative with the condition. The incidence of autoimmune diseases is higher in patients and relatives of those with vitiligo, and vitiligo often has an early onset in these individuals. Exposure to certain chemicals has also been implicated as a risk factor for vitiligo, including substances

like monobenzyl ether of hydroquinone, rhododendrol, and other phenols. The use of hair dyes has also been associated with an increased risk of developing vitiligo [6].

5. Precipitating Factors of Vitiligo

Identifying precise triggering factors for vitiligo is challenging. However, it is important to consider the history of emotional or physical stress, physical illness, oral medications (such as chloroquine and clofazimine), infections, severe sunburn, or repeated trauma/injury (known as Koebner's phenomenon) that preceded the development of vitiligo lesions. During times of war, vitiligo has been frequently observed. Many vitiligo patients can attribute the onset of their condition to a specific life event, crisis, or illness. Some individuals may experience the onset of vitiligo following a physical injury or sun exposure, which is known as the Isomorphic Koebner Phenomenon [7].

6. Theories Involved in Vitiligo Pathogenesis

Hypothesis/Theories	Description
Genetic Hypothesis	- Familial occurrence and 6-8% risk for first-degree relatives - Susceptibility loci, including TYR gene, indicate genetic dysregulation
Autoimmune Hypothesis	- Inflammatory cell infiltration in vitiligo lesions - Elevated antibody levels and increased frequency of autoimmune disorders
Biochemical Theory	- Dysregulation of bipterin pathways - Elevated levels of pteridines observed in vitiligo
Oxidative Stress Hypothesis	- Abnormally low levels of catalase enzyme - Disrupted melanin synthesis pathways and mitochondrial ROS production
Decreased Melanocyte Survival Hypothesis	- Deficiencies in survival signals for melanocytes - Decreased expression of c-kit receptors and lower SCF expression
Melanocytorrhagy Hypothesis	- Weakly anchored melanocytes susceptible to detachment - Elevated levels of tenascin inhibiting melanocyte adhesion
Zinc-α2-Glycoprotein Deficiency Hypothesis	- Decrease in ZAG impairing melanocyte adhesion
Microbial Hypothesis	- Connection between vitiligo and certain infections - Association with HCV, CMV, H. pylori infections, and antibacterial serum titers
Intrinsic Theory	- Inherent defects in melanocytes contributing to their death
Integrated Theory (Convergence Theory)	- Multiple pathological pathways interacting to contribute to vitiligo development

7. Pathophysiology of Metabolic Disorders in Vitiligo:

The pathophysiology of metabolic disorders in vitiligo is a complex process involving genetic, immunological, autoimmunological, cytotoxic, neuronal, and inflammatory factors. This complexity may explain the wide range of systemic manifestations observed in vitiligo patients [8].

Vitiligo is associated with the production of autoantibodies, leading to the development of autoimmunological comorbidities such as alopecia areata, autoimmune thyroid disease, Addison's disease, pernicious anemia, type I diabetes mellitus, and myasthenia gravis.

Inflammatory factors, including proinflammatory cytokines like tumor necrosis factor, interleukin 1, and interleukin 6, are also involved in vitiligo and can contribute to insulin resistance, metabolic complications, and atherosclerosis [9].

Homocysteine, which inhibits tyrosinase and increases cardiovascular risk, may play a role in the metabolic disturbances observed in vitiligo patients. Higher homocysteine levels and lower vitamin B12 concentrations have been found in vitiligo patients and are correlated with the severity of the disease. Additionally, the role of melanocytes in metabolic disorders is worth investigating, as

they have been found in various tissues, including adipose tissue, where they have anti-inflammatory and antioxidant effects. Reduced melanocyte function in adipose tissue may lead to increased production of reactive oxygen species, contributing to metabolic syndrome in vitiligo [10].

8. Classification

In 2011, a global accord separated SV from all other types of vitiligo and classified

vitiligo as all forms of NSV. Mixed vitiligo is a subtype of NSV characterized by the coexistence of SV and NSV in the same individual (Table 1). One of the most important results of the agreement was to distinguish SV from other types of vitiligo, especially in light of its prognostic implications [11].

Table (1) Classification of vitiligo [12].

Type of vitiligo	Subtypes
Non-Segmental Vitiligo	<ul style="list-style-type: none"> • Acrofacial, • Mucosal (more than one site affected), • Generalized or common, <ul style="list-style-type: none"> • Universal, • Rare variants of vitiligo (leukoderma punctata, hypochromic vitiligo, follicular vitiligo) <ul style="list-style-type: none"> • Focal
Segmental Vitiligo	<ul style="list-style-type: none"> • Unsegmented • Bi- or multisegmented
Mixed (NSV + SV)	<ul style="list-style-type: none"> • Concomitant occurrence of SV and NSV According to severity of SV
Unclassified	<ul style="list-style-type: none"> • Focal at onset, multifocal asymmetrical nonsegmental, <ul style="list-style-type: none"> • mucosal (one site)

Nonsegmental vitiligo encompasses various subtypes, including acrofacial, mucosal, widespread, universal, mixed, and less common forms. The most common subtypes of nonsegmental vitiligo are generalized and acrofacial. Generalized vitiligo is characterized by the symmetrical and

bilateral distribution of depigmented macules or patches across the entire body. These patches occur randomly and are commonly found in areas prone to pressure, friction, or trauma. The onset of generalized vitiligo can occur during childhood or early adulthood [13].

Figure 1



Fig. (1) Generalized vitiligo, bilateral, often symmetrical, depigmented macules or patches [14].

Acrofacial vitiligo is characterized by the presence of depigmented macules on the face and extremities. It has the potential to spread to other body areas and progress into a

generalized or universal condition. In cases of lip-tip vitiligo, the lesions are confined to the lips and fingertips [15]. **Figure 2**



Fig. (2) Acrofacial vitiligo, depigmented macules limited peri-orificial areas, distal extremities and/or the face [14].

Mucosal vitiligo specifically affects the oral and/or genital mucosa and may occur in conjunction with generalized vitiligo or develop independently. If it stays isolated after at least two years of observation, it is categorized as unclassified mucosal vitiligo. Vitiligo universalis (**Figure 3**) refers to

extensive depigmentation of the skin, covering approximately 80-90% of the body surface. Typically, it goes from widespread vitiligo to whole or near-total depigmentation of the skin and hair [16].



Fig. (3) Vitiligo universalis, complete or nearly complete depigmentation of the skin [14].

Focal vitiligo is characterized by a small, localized area of depigmentation that remains stable for one to two years. It can evolve into either segmental vitiligo (SV) or nonsegmental vitiligo (NSV). Mixed vitiligo refers to the simultaneous presence of SV and NSV, where depigmented patches in a segmental distribution are absent at birth, NSV develops after SV, and there is a differential response to narrow-band ultraviolet B (NB-UVB) therapy. The coexistence of SV and NSV suggests a generalized polygenic condition, where segmental involvement precedes the generalization of the disease and is often more resistant to treatment [17].

In some cases, vitiligo does not fit into the typical categories of SV or NSV. Punctate vitiligo is characterized by small macules, measuring between 1 and 1.5 mm in diameter, that can appear anywhere on the body. These macules, without specific vitiligo lesions, are referred to as "leukoderma punctata." Hypochromic or mild vitiligo is characterized by scattered hypopigmented macules that occur seborrheically on the face, neck, trunk, and scalp. This type of vitiligo seems to affect individuals with darker skin tones exclusively [18]. **Figure 4**



Fig. (4) Hypochromic vitiligo, hypopigmented macules of the trunk and scalp distributed in a seborrheic pattern [14].

Typically, segmental vitiligo is accompanied by leukotrichia (white hair) and a quick start. The lesions resemble nonsegmental vitiligo lesions in that they are white and have clear edges. One or more depigmented macules on one side of the body, often affecting the head, trunk, limbs, extremities, and neck,

characterize monosegmental vitiligo. Depigmentation often develops on the afflicted region between six and twenty-four months, and the patches commonly remain. Infrequently, the lesions may return or spread, resulting in mixed vitiligo [19]. **Figure 5**



Fig. (5) Monosegmental vitiligo of the left abdomen, depigmented patches are usually confined to a single dermatome, with partial or complete involvement [14].

9. Diagnosis

Typically, vitiligo is diagnosed with a clinical examination involving the identification of particular features. These include the existence of acquired, amelanotic, non-scaly, chalky-white macules with defined edges in periorificial regions, lips, distal extremity tips, the penis, segmental patterns, and sites of friction. Laboratory tests are typically unnecessary for making a diagnosis, however they may be utilized to rule out other conditions. In situations requiring confirmation, in vivo confocal microscopy or a skin biopsy can detect the lack of melanocytes

in the afflicted region. A histological investigation indicates a total lack of melanin pigment and melanocytes in the epidermis. The use of a Wood's lamp, which emits UV radiation, can aid in the detection of depigmentation that is not evident to the human eye. By measuring perifollicular pigmentation and telangiectasia, dermoscopy provides an additional method for identifying vitiligo from other depigmenting illnesses. To establish an accurate diagnosis, it is essential to distinguish vitiligo from melanoma-associated leukoderma, nevus depigmentosus, and other depigmentation illnesses [20].

10. Clinical assessment

The initial evaluation of a vitiligo patient plays a crucial role in guiding effective treatment. To assess the severity of the disease and prognostic factors, it is necessary to gather a comprehensive medical history and conduct a thorough examination of the skin. The Vitiligo European Task Force has developed an assessment form that encompasses personal and family history elements, along with clinical examination items, to assist in the evaluation process. Key factors to consider during the assessment include a family history of vitiligo and premature hair graying, personal or family history of thyroid disease or other autoimmune conditions, skin phototype, disease duration, extent and activity of the lesions, rate of lesion progression, presence of Koebner's phenomenon (the development of vitiligo following mechanical trauma), halo nevi, previous treatments and their effectiveness, episodes of repigmentation, occupational history, and the impact of the disease on the patient's quality of life. Patients with high scores on the Koebner's phenomenon in vitiligo score (K-VSCOR) should be advised to minimize mechanical stress on areas susceptible to this phenomenon. Furthermore, the Vitiligo Area Scoring Index (VASI) can be utilized to quantitatively assess the extent of vitiligo in different body regions by assigning a percentage based on the degree of depigmentation [21].

11. Treatment

Treatment of vitiligo involves a comprehensive approach aimed at halting disease progression, promoting repigmentation, and addressing the psychosocial impact of the condition. The therapeutic options for vitiligo include topical corticosteroids, topical calcineurin inhibitors, topical vitamin D analogs, and topical immunomodulators, which can be effective in limited and localized disease. Phototherapy, such as narrowband ultraviolet B (NB-UVB) and psoralen plus ultraviolet A (PUVA), is widely used and can achieve repigmentation in a significant proportion of patients. Surgical interventions, such as autologous melanocyte transplantation and suction blister grafting, are considered in stable vitiligo with limited involvement. Emerging treatments, including Janus kinase inhibitors and targeted immunomodulators, show promise in modulating the immune response and promoting repigmentation. Psychological support and counseling are integral components of vitiligo management, given the psychosocial impact of the condition. A tailored and individualized treatment approach,

considering the extent, activity, and patient preferences, is crucial in optimizing outcomes and improving the overall well-being of individuals with vitiligo [22].

12. Conclusion

Vitiligo is a complex and heterogeneous disorder with a wide range of clinical manifestations. Although the exact etiology remains elusive, advancements in research have shed light on the involvement of immune dysregulation, oxidative stress, and genetic predisposition in the pathogenesis of vitiligo. Diagnosis of vitiligo is primarily clinical, based on characteristic depigmented macules, while further investigations may be warranted to exclude other conditions. Management of vitiligo involves a multidisciplinary approach, including topical therapies, phototherapy, surgical interventions, and psychological support. While repigmentation outcomes vary, advancements in targeted therapies and immunomodulatory agents hold promise for future treatment strategies.

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