Section A-Research paper

An Outline of Vitiligo; Types, Pathogenesis and Diagnosis

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Abstract

Background: Vitiligo is a disease in which destruction of skin melanocytes results in hypopigmented or depigmented skin patches, The loss of melanin is in the skin but partly also in mucous membranes, various mechanisms have been implicated to explain melanocyte destruction, including genetic predisposition, environmental triggers (such as friction), metabolic alteration and altered inflammatory and immune responses. It is classified into 3 types, that is, non-segmental, segmental, and undetermined/unclassified vitiligo, the uniform classification of vitiligo is very important in predicting its clinical course and prognosis and communication among researchers. Generally, vitiligo can be diagnosed depending on clinical features. While biopsy is usually not required, it may be useful in individual cases for differential diagnosis. vitiligo is a multifactorial disorder characterized by the loss of functional melanocyte, multiple mechanisms have been proposed for melanocyte destruction in vitiligo. These include genetic, autoimmune responses, oxidative stress, generation of inflammatory mediators and melanocyte detachment mechanisms, none of these proposed theories are in themselves sufficient to explain the different vitiligo phenotypes; and the overall contribution of each of these processes is still under debate, although there is now consensus on the autoimmune nature of vitiligo. The Vitiligo Area Severity Index (VASI) and Vitiligo European Task Force (VETF) were considered as responsive and reliable tools to assess the extent of depigmentation in patients with vitiligo. The diagnosis of vitiligo is generally straightforward, made clinically based upon the finding of acquired, amelanotic, nonscaly, chalky-white macules with distinct margins in a typical distribution: periorificial, lips and tips of distal extremities, penis, segmental and areas of friction.

Keywords: Vitiligo

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Introduction

Vitiligo is a disease in which destruction of skin melanocytes results in patches of white skin and hair, The loss of melanin is in the skin but partly also in mucous membranes, various mechanisms have been implicated to explain melanocyte destruction, including genetic predisposition, environmental triggers (such as friction), metabolic alteration and altered inflammatory and immune responses**.** It affects 1% of the world's population without any significant difference in prevalence due to sex, ethnicity, or geographic region**.** Males and females have equal affection, although women and girls often seek consultation more frequently, possibly due to the greater negative social impact than for men and boys (**1**).

The term leucoderma is applied to depigmented patches of known aetiology as those following burns, contact with chemicals like phenol or following an inflammatory skin disease. As opposed to vitiligo, it doesn't progress after removal of the cause **(2).**

Classification of vitiligo

It is classified into 3 types, that is, non-segmental, segmental, and undetermined/unclassified vitiligo, the uniform classification of vitiligo is very important in predicting its clinical course and prognosis and communication among researchers **, (3).**

Distinguishing SV from other types of vitiligo was one of the most important decisions of the consensus, primarily because of its prognostic consequences.

Table (1): **Classification of vitiligo (3).**

Non-segmental vitiligo (NSV)	**Focal vitiligo** refers to an acquired small, isolated, depigmented lesion without an obvious distribution pattern
	Mucosal vitiligo typically involves the oral and/or genital mucosae. It may occur as an isolated condition
	Acrofacial vitiligo is characterized by depigmented macules limited to the face, head, hands, and feet. The lip-tip variety is a subcategory of the acrofacial type in which lesions are restricted to the cutaneous lips and distal tips of the digits.
	Generalized vitiligo It is characterized by bilateral, often symmetrical, milky-white macules or patches occurring in a random distribution over multiple parts of the body
	Vitiligo universalis refers to complete or nearly complete depigmentation of the skin (80%–90% of body surface).
Segmental (SV)	**Focal**
	Mucosal
	Unisegmental: The most common form of SV, one or more white depigmented macules are distributed on one side of the body
	Bi- or multisegmental: Depigmented patches overlapping several ipsi or contralateral dermatomes or occurring on large areas delineated by Blaschko's lines.
Mixed (NSV+SV)	Refers to the association of initial SV followed by the occurrence of bilateral NSV lesions several months or, more rarely, years later. Leukotrichia and halo nevi at onset may be predictors for developing MV in patients with SV.
Unclassified	**Multifocal asymmetrical nonsegmental**
	Mucosal (one site)
	Focal at onset

Several conditions are difficult to classify into the two classical forms of NSV and SV.:

- **Punctate vitiligo** refers to sharply demarcated depigmented punctiform 1- to 1.5-mm macules involving any area of the body, if these lesions do not coexist with classical vitiligo macules, they should be referred to as "leukoderma punctata." **(3).**
- **Hypochromic vitiligo** in which hypopigmented macules in a seborrheic distribution on the face and neck associated with hypopigmented macules of the trunk and scalp **(4).**
- **Follicular vitiligo** presents with leukotrichia in the absence of depigmentation of the surrounding epidermis **(5).**

Table (2): Differentiation between Clinical subtypes of vitiligo (6)

Segmental vitiligo	Non-Segmental vitiligo
Begins often in the childhood	Later onset
Rare Autoimmunity	Associated autoimmunity
Frequently facial	Trauma prone sites and +ve koebnerization
Stable, good response to autologous grafting	Unstable, relapses after autologous grafting
Dermatomal, unilateral distribution	Non-dermatomal, bilateral distributio

Differential Diagnosis of Vitiligo:

Generally, vitiligo can be diagnosed depending on clinical features. While biopsy is usually not required, it may be useful in individual cases for differential diagnosis **(7).**

Many disorders can mimic vitiligo, especially early vitiligo. A useful clinical approach is to classify them based on lesions extension (localized or widespread), lesions patterns (eg, guttate/confetti) and the degree of pigment loss (depigmented or hypopigmented). Further clinical differentiation can be made on the basis of associated morphologic signs, including secondary changes of the epidermis (such as scaling and atrophy) and dermis (such as induration and infiltration **(8)**

Table (3): Differential diagnosis of vitiligo (3).

Chemically induced leukoderma (often occupational)	• Arsenic • Phenols and other derivatives	• catechols
Infections	• Leishmaniasis (post-kala-azar) • Leprosy • Onchocerciasis	• Secondary syphilis • Treponematoses (pinta and syphilis) • Tinea versicolor
Genetic syndromes	• Chédiak–Higashi syndrome • • Hypomelanosis of Ito • Oculocutaneous albinism	• Tuberous sclerosis • Vogt–Koyanagi–Harada syndrome • Waardenburg syndrome • Piebaldism
Post-inflammatory hypopigmentation	• Atopic dermatitis/allergic contact dermatitis • Nummular dermatitis	• Pityriasis alba • Post-traumatic hypopigmentation (scar) • Psoriasis • Sarcoidosis

	• Phototherapy and radiotherapy-induced hypopigmentation	• Systemic lupus erythematosus • Topical or systemic drug-induced depigmentation
Neoplastic	• Amelanotic melanoma • Halo nevus	• Melanoma-associated leukoderma • Mycosis fungoides
Idiopathic	• Idiopathic guttate hypomelanosis • Lichen sclerosus et atrophicus • Lichen striatus-like leukoderma	• Morphea • Melasma (caused by contrast between lighter and darker skin) Progressive (or acquired) macular hypomelanosis
Malformations	• Nevus anemicus	• Nevus depigmentosus/hypopigmentosu
Nutritional	• Kwashiorkor	• Melanoma-associated leukoderma • Mycosis fungoides

Associations:

Many studies have demonstrated the associations of vitiligo with thyroid disorders and other associated autoimmune diseases, such as alopecia areata, rheumatoid arthritis, adult-onset diabetes mellitus, Addison's disease, pernicious anemia, systemic lupus erythematosus, psoriasis, and atopic background **(4).**

Many disorders and syndromes are associated with vitiligo. Selected vitiligo subjects can be affected by multisystem organ dysfunction, the ―vitiligo systemic syndromes‖. Most of those cases are discovered at birth or during infancy **(9).**

(Table 4) Disorders and syndromes possibly associated with vitiligo:

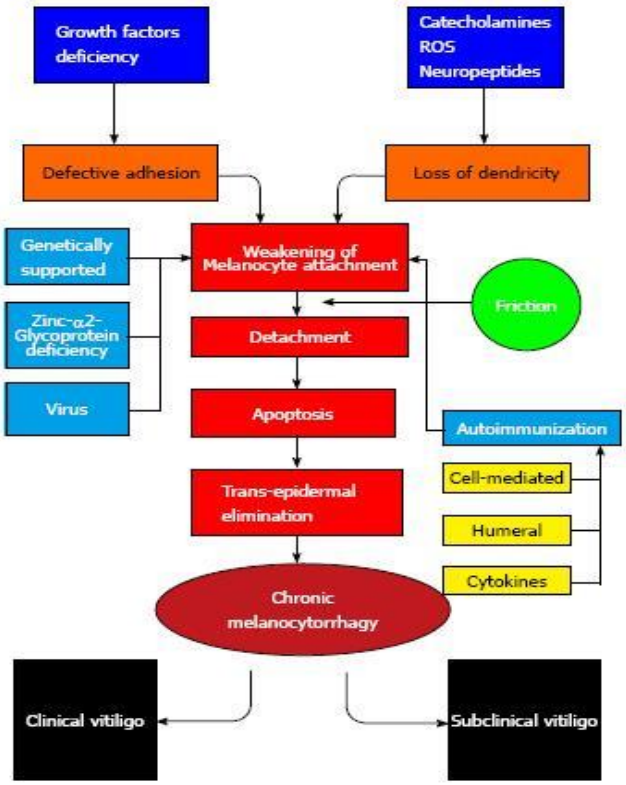
More Common association	Addison'sdisease Alopecia areata Atopic dermatitis Autoimmune thyroid disease Chronic urticaria Diabetes mellitus Halo nevi Morphea Multiple sclerosis Hypoparathyroidism	Ichthyosis Lymphoma Melanoma Mitochondrial myopathy, encephalopathy, lactic stroke (MELAS) syndrome Myasthenia gravis non-melanoma skin cancer Nail dystrophy acidosis, and Ocular abnormalities	Pemphigus vulgaris Pernicious anemia Psoriasis Rheumatoid-arthritis Sarcoidosis Schmidt syndrome Systemic-lupus erythematosus Turner syndrome Twenty-nail dystrophy Vogt– Koyanagi–Harada syndromde

Less common associations	Acrokeratosis Paraneoplastica of Bazex Alezzandrini syndrome Asthma Ataxia-telangiectasia	APECED syndrome (Autoimmune polyendocrinopathy candidiasis ectodermal dysplasia) Deafness Dysgammaglobulinemia	Hemolytic anemia (autoimmune) Hepatitis C HIV Inflammatory bowel disease Kabukisyndrome Kaposi sarcoma

Aetiopathogenesis:

vitiligo is a multifactorial disorder characterized by the loss of functional melanocyte, multiple mechanisms have been proposed for melanocyte destruction in vitiligo. These include **genetic, autoimmune responses, oxidative stress, generation of inflammatory mediators and melanocyte detachment mechanisms**, none of these proposed theories are in themselves sufficient to explain the different vitiligo phenotypes; and the overall contribution of each of these processes is still under debate, although there is now consensus on the autoimmune nature of vitiligo **(3).**

Several mechanisms might be involved in the progressive loss of melanocytes and they consist either of immune attack or cell degeneration and detachment. **The "convergence theory" or "integrated theory"** suggests that multiple mechanisms may work jointly in vitiligo to contribute to the destruction of melanocytes, ultimately leading to the same clinical result **(10).**



(Figure 1) Vitiligo pathogenesis (11).

1. Genetics of vitiligo:

Vitiligo is inherited in a non-Mendelian, multifactorial, and polygenic pattern **(12).**

Vitiligo is genetically complex, involving polygenic risk from at least 50 susceptibility loci identified by genome-wide association studies of European-derived white subjects, as well as environmental triggers that remain unknown. Most of the loci that have been associated with vitiligo encode genes involved in immunoregulation, apoptosis, and melanocyte biology **(13).**

In addition, individuals who had first-degree relatives with vitiligo were noted to have a high risk for developing the disease: approximately 6% compared to 1% or less in the normal population **(13).**

Confirming an important role for genetic factors in vitiligo, the twin concordance rate was found to be 23%. But since the twin concordance is not 100%, this simultaneously emphasized the contributory significance of other factors. Current understanding suggests that complex interactions of genetic,environmental, and other factors account for development of vitiligo **(14).**

Indeed, the variants with the greatest overall impact on disease risk genome-wide reside within transcriptional enhancers located in the class I and class II regions of the major histocompatibility complex (MHC) on chromosome 6**.** Polymorphisms in HLA-A discuss the most significant genetic risk of vitiligo **(13).**

2. Autoimmune Hypothesis:

The autoimmune hypothesis is primarly based on the association of vitiligo with known autoimmune diseases and the presence of organ specific antibodies in affected patients. Another common finding that supports this hypothesis is that vitiligo often responds to immuno-suppressive treatments. the mechanisms of immunity are innate, adaptive (humoral (antibody-mediated), cell-mediated, or mediated by cytokines) **(14).**

A) Innate immunity:

Innate immunity bridges the gap between oxidative stress and adaptive immunity in vitiligo**.** Innate immune cells are probably activated early on in vitiligo, by sensing exogenously or endogenously induced stress signals released from melanocytes and keratinocyte with subsequent activation of adaptive and memory immune responses **(3).**

Furthermore, patients with vitiligo were found to have increased presence of type-1 innate lymphoid cells (NK and ILC1)-producing interferon-gamma (IFNγ) in the blood and in non-lesional skin of vitiligo patients **(15)**

B) Adaptive immunity:

Both humoral and cell-mediated immune dysregulations are involved in the pathogenesis of vitiligo.

- **Humoral Immunity:**

Patients with vitiligo were found to have antibodies to surface and cytoplasmic melanocyte antigens **(3).**

Overexpression of the B lymphocyte-activating factor may activate self-reactive B cells to produce autoantibodies against melanocytes with the interaction of both CD4+ and CD8+ T cells subsequently causing autoimmune vitiligo **(3).**

Therefore, both humoral and cell-mediated immunities are supposed to have a role in the pathogenesis of vitiligo **(16).**

However, autoantibody titres do not correlate with vitiligo activity and whereas the presence of antibodies is systemic, vitiligo develops in well-defined macules**,** suggesting that anti-melanocyte antibodies are not the main driver in vitiligo pathogenesis **(17).**

❖ **CD8+ T cells are responsible for destruction of melanocyte in vitiligo lesions:**

Cytotoxic CD8+ T cells that target melanocytes specifically are responsible for the destruction of melanocytes. They infiltrate the perilesional skin, where vitiligo is most active, preferentially localize to the epidermis and dermis, adjacent to melanocytes. these cytotoxic CD8+ T cells are found in higher numbers in the blood of patients with vitiligo compared with healthy controls; and these numbers correlate with vitiligo activity **(18).**

Melanocyte destruction was found to be associated with the prominent presence of CLA+ T cells at the perilesional site, the majority of which expressed perforin and granzyme-B.

several cytokines are produced by the CD8+ T cells in vitiligo lesions and include interferon-γ (IFNγ) and tumor necrosis factor (TNF) among others **(19).**

❖ **The role of cytokines (Impaired Cytokine Theory):**

Cytokines have crucial functions in the development, differentiation, and regulation of immune cells, thus leading to autoimmunity **.** Increased levels of a class of proteins called interleukins (ILS) might be linked to the active stage of vitiligo. for example, it has been reported that there is a positive correlation between elevated serum and lesional skin IL-17 levels, and the extent of the depigmentation patch area in vitiligo **(20).**

Several studies investigated the assumed role of cytokines in vitiligo by studying IL-17, IL-10, IL-2 and IL-6**.** Increased concentrations of serum IL-10, IL-13, and IL-17A and decreased concentrations of transforming growth factor (TGF)-B1 which is required for the maturation of Treg cells, suggested altered cell-mediated immunity that may facilitate the melanocyte cytotoxicity in vitiligo. Elevated production of IL-6, a cytokine that induces intercellular adhesion molecule-1 (ICAM-1) expression, facilitating leukocyte–melanocyte interactions, and IL-8, an attracting cytokine to neutrophils by mononuclear cells have been found in vitiligo patients **(21).**

Studies had found a significantly higher expression of proinflammatory cytokines with an inhibitory effect on pigmentation, such as IL-6 and TNF-α, in lesional and perilesional skin in vitiligo patients, while melanogenic mediators such as granulocyte– monocyte colony stimulating factor (GM-CSF), basic fibroblastic growth factor (bFGF), stem cell factor (SCF) and endothelin-1 (ET1) were found to have significantly lower expression **(22).**

❖ **Cytokines exhibit a complex network of autocrine and paracrine regulation of other cytokines. For example:**

IL-17A has been shown to extensively upregulate IL-6, IL-1β and Tumor necrosis factor (TNF)-α production in fibroblasts and keratinocytes of the skin, IL-17 can dramatically amplify the inhibitory effect of TNF-α on melanogenesis. Interferon (IFN)-γ and IL-17A increased the synthesis of an anti-melanogenic cytokine IL-6 in Normal Human Melanocytes (NHM). IL-23 Receptor (IL-23R) is expressed by inflammatory macrophages, which are activated to produce IL-1, TNF-α, and IL-23 itself. IL23 induces the differentiation of Th17 cells in a proinflammatory context, especially in the presence of TGF-β and IL-6 **(23).**

❖ **The IFN-γ–CXCR3-CXCL9/10 axis is central for T cell recruitment and function:**

Interferon-γ is central to vitiligo pathogenesis and promotes auto-reactive CD8+ T cell recruitment into the skin through a feedback loop.134 The IFNγ-induced CXC chemokine-ligand 9 (CXCL9), CXCL10and CXCL11 were the most highly expressed genes in a transcriptional profile of lesional skin of vitiligo patients. whereas CXCL10 which is induced by INF-γ is a potential bio marker that can demarcate between stable and active vitiligo **(24).**

❖ **The IFN-γ receptor recruits JAK1 AND JAK2 kinases:**

Interferon-γ signals by binding to its cell surface receptor (IFNgR), which forms a heterodimeric protein complex which recruits JAK1 and JAK2 kinases, leading to phosphorylation and nuclear transloca-tion of STAT, which in turn transcriptionally activates downstream IFN-γ-inducible genes **(25).**

JAK1 expression is much more intense and diffuse in lesional skin from patients with vitiligo compared with healthy tissue. High JAK1 expression is associated with short dis-ease duration and lower percentage of surviving melanocytes. All these findings support the investigation of therapies that disrupt the IFN-γ–CXCR3-CXCL9/10 axis and the downstream signalling proteins JAK1, JAK2, STAT1 **(26).**

❖ **Autoimmune resident memory T cells are responsible for vitiligo relapse:**

Relapses of vitiligo after successful repigmentation is common with an estimated risk of 40% within the first year. Functional CD8 tissue-resident memory T cells (T_{RM}) were found in both stable and active vitiligo, suggesting that the T_{RM} which remain in stable disease could be responsible for vitiligo reactivation **(3).**

The primary role of T_{RM} seems to be sentinels that recruit effector cells from the circulation **(27).**

T_{RM} are believed to be responsible for long-term maintenance and potential relapse of vitiligo in human patients through cytokine-mediated recruitment of T cells from the circulation **(27).**

Targeting TRM cells has thus been suggested as a potential therapeutic strategy to durably reverse vitiligo **(3).**

an increasing number of studies are reporting the involvement of several cytokines during T_{RM} cell differentiation, homeostasis, or regulation. Among all these pro-inflammatory cytokines, IL-15 is of particular interest **(28)**

3.Oxidative stress and intrinsic abnormalities of melanocytes and keratinocytes

Research into the pathogenesis of vitiligo suggests that oxidative stress may be the initial event in the destruction of melanocytes **(29).**

Melanocytes respond to stress by releasing reactive oxygen species (ROS). This causes an imbalance between pro-oxidants (superoxide dismutase, malondialdehyde, xanthine oxidase) and enzymatic and nonenzymatic anti-oxidants (catalase, glutathione reductase, glutathione peroxidase, thioredoxin reductase and thioredoxin, superoxide dismutases, and the repair enzymes methionine sulfoxide reductases A and B) in the skin and in the blood **(3).**

The production and accumulation of ROS triggers DNA damage, protein oxidation and fragmentation, and lipid peroxidation, which compromises cellular function.

ROS upregulates TNF α and other proinflammatory cytokines such as TGF β (which play a role in the inhibition of melanogenesis) and IL 2 **(30).**

Oxidative stress was also shown to be responsible for decreased melanocyte adhesiveness at the borders of lesions, possibly explaining the Koebner phenomenon **(3).**

Altered E-cadherin expression levels in melanocytes have been found in vitiligo skin prior to the development of depigmentations. Deficient E-cadherin expression leads to the loss of epidermal melanocyte adhesion during oxidative or mechanical stress. Loss of melanocytes from the epidermal layer could be an early phenomenon in vitiligo. Oxidative stress alters the WNT pathway, which is involved in melanocyte differentiation by decreasing WNT expression and activation in keratinocytes and melanocytes specifically in vitiligo skin **(31).**

3.Damage-Associated Molecular Patterns (DAMPs):

Cellular stress may push melanocytes to secrete exosomes which contain melanocyte-specific antigens, miRNAs, heat shock proteins and damage-associated molecular patterns (DAMPs). DAMPs activate dendritic cells to produce proinflammatory cytokines**.** The heat shock protein HSP70i is known as the main DAMP involved in the pathogenesis of this disease. Chemically induced cellular stress also intensifies the synthesis of the receptor NLRP3 participating in the activation of the inflammasome or the cytokine IL-1β directly. This is followed by cytokine- and chemokine-driven activation of T helper 17 cells and the dysfunction of T regulatory cells. Overexpression of the gene encoding the receptor NLRP1 (Langerhans cells) leads to the activation of inflammasome and induces the conversion of pro-IL-1β into active IL-1β, which is involved in the pathogenesis and progression of vitiligo **(31).**

4. Zinc-α2-glycoprotein (ZAG) deficiency hypothesis:

Few authors have pointed towards the role of zinc-α2-glycoprotein (ZAG) in the pathogenesis of vitiligo. They hypothesize that lack of ZAG causes impaired melanocytic adhesion to other cells in the epidermis **(11).** The efficacy of zinc in the treatment of vitiligo may be due to its ability to precipitate ZAG at the site of vitiligo **(32).**

5.Viral theory:

Various types of viral infection may induce the induction of vitiligo, as the DNA of cytomegalovirus has been observed in skin biopsy in patients with vitiligo. As well, hepatitis C virus and the Epstein–Barr virus might be a causative factor in the initiation of the pathogenesis of vitiligo**.** Interestingly, a recent study found varicella-zoster virus (VZV) virions in actively spreading SV skin, suggesting a potential involvement of VZV in SV pathogenesis **(33).**

6. The Neural Theory:

Certain peripheral chemical neurotransmitters such as neuropeptide Y are increased peripherally leading to the destruction of melanocytes. Furthermore, the degeneration of axons and Schwann cell has been reported to be linked with the induction of vitiligo**.** According to neural theory, melanocyte death in non-segmental vitiligo (NSV) is caused directly or indirectly by an inappropriate reaction of the neural-crest-derived pigment cells to neuropeptides, catecholamines or their metabolites, or more generally to an overactive sympathetic system **(34).**

7. Cellular, molecular and biochemical alterations and functional melanocytes loss of in vitiligo:

A) Apoptosis and accelerated cell senescence:

Vitiligo melanocytes seem to be defective in activating autophagy, a process that prevents oxidative damage and maintains the proliferative capacity of melanocytes **(24).**

B) Melanocytorrhagy theory (Adhesion theory):

Adhesion defects of melanocytes lead to migration of melanocytes through the epidermal basal layer, causing T-cells activation by melanocytes auto-antigens and subsequent melanocytes injury and hypopigmentation. Remarkably, **Ricard et al., (35)** illustrated that discoidin domain receptor 1, which is an adhesion molecule of melanocytes is diminished in vitiligo.

Assessment methods for the evaluation of vitiligo:

The Vitiligo Area Severity Index (VASI) and Vitiligo European Task Force (VETF) were considered as responsive and reliable tools to assess the extent of depigmentation in patients with vitiligo **(34).**

Scores designed for the assessment of vitiligo:

Vitiligo Area Severity Index (VASI):

Its name is an adoption from PASI score in psoriasis. The percentage of vitiligo involvement is calculated in terms of hand units. One hand unit is approximately equivalent to 1% of the total body surface area **(36).**

The degree of pigmentation is estimated to the nearest of one of the following percentages:

- 100% - complete depigmentation, no pigment is present.
- 90% - specks of pigment present.
- 75% - depigmented area exceeds the pigmented area.
- 50% - pigmented and depigmented areas are equal.
- 25% - pigmented area exceeds depigmented area.
- 10% - only specks of depigmentation present.

The VASI for each body region is determined by the product of the area of vitiligo in hand units and the extent of depigmentation within each hand unit measured patch. Total body VASI = summation of all body sites (Hand Units) × (Residual depigmentation) **(37).**

- Face and neck can be assessed separately.
- One hand unit, which encompasses the palm plus the volar surface of all digits, is approximately 1% of the total body surface area.
- The extent of residual depigmentation within each hand unit measured patch (possible values of 0, 10%, 25%, 50%, 75%, 90%, 100%)

Vitiligo European Task Force (VETF):

VETF is a system that incorporates three components of vitiligo: extent, stage and progression of disease**, (38).**

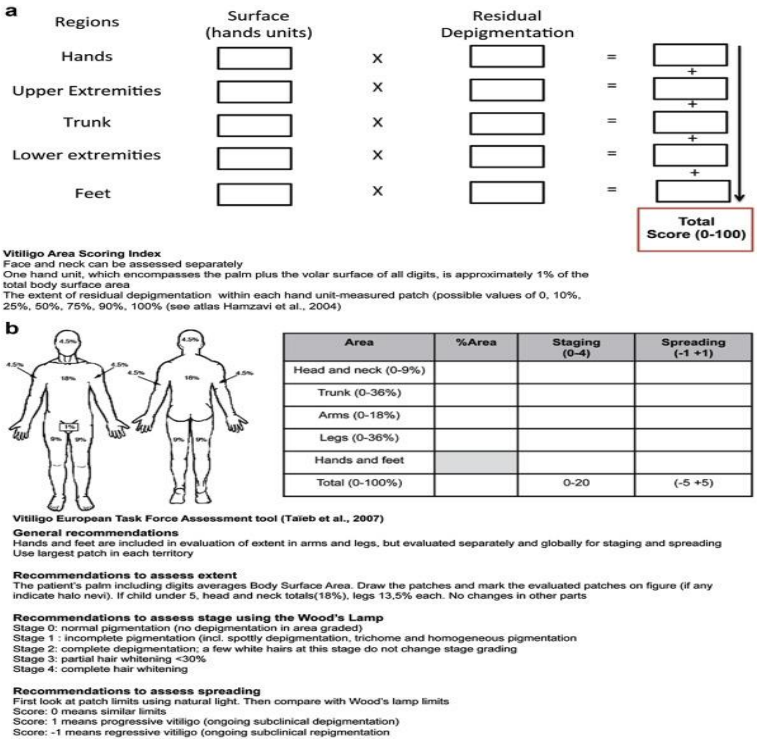


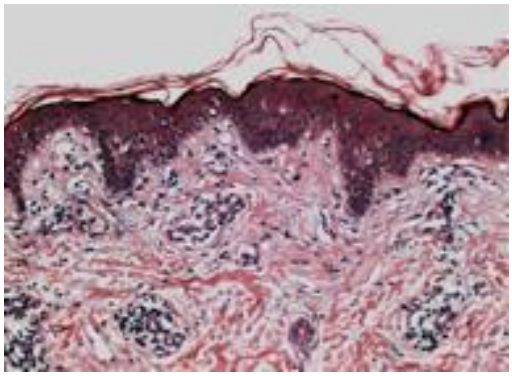
Figure (2) Scores used for assessment of vitiligo (28)

Diagnosis:

The diagnosis of vitiligo is generally straightforward, made clinically based upon the finding of acquired, amelanotic, nonscaly, chalky-white macules with distinct margins in a typical distribution: periorificial, lips and tips of distal extremities, penis, segmental and areas of friction **(39).**

Wood's lamp examination helps visualize vitiligo through the accentuation of lesions, especially in light-skin individuals. Experienced dermatologists utilize Wood's light and dermoscopy to differentiate between stable and active disease. Wood's light accentuates the objective activity signs: confetti-like lesion, hypochromic borders, and koebnerization, which is subtle under room light in lighter skin phototype individuals. However, clinicians need to familiarize with the autofluorescence in vitiligo lesions compare to other hypopigmentary diseases and skin dyschromia **(33).**

The diagnosis of vitiligo does not usually require confirmatory laboratory tests. A skin biopsy or other tests are not necessary except to exclude other disorders. The absence of melanocytes in a lesion can be assessed non-invasively by in vivo confocal microscopy or by a skin biopsy. The histology of the centre of a vitiligo lesion reveals complete loss of melanin pigment in the epidermis and absence of melanocytes. Occasional lymphocytes may be noted at the advancing border of the lesions **(40).**



(Figure 3) Active vitiligo. Perivascular lymphocytic infiltrate, with epidermal aggression and basal layer vacuolar degeneration foci (Hematoxylin &eosin, ×40) **(41).**

Dermoscopy can be used to differentiate vitiligo from other depigmenting disorders. More importantly, it can be useful in assessing disease activity in vitiligo and the stage of evolution: progressive lesions display perifollicular pigmentation, whereas stable or remitting lesions display perifollicular depigmentation **(42).**

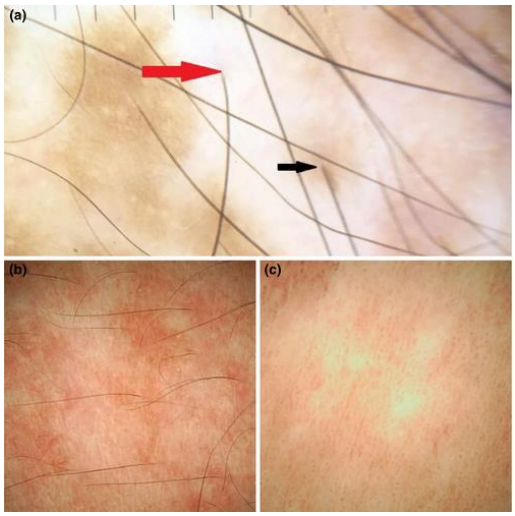


Figure (4): Representative dermoscopic image from a vitiligo lesion (polarized ×10) showing (a) perifollicular pigmentation (black arrow) and perifollicular depigmentation (red arrow), and altered pigment network: (b) reduced pigment network, and (c) absent pigment network **(42).**

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