Chapter

Vitiligo: Pathogenesis, Clinical Features, and Treatment

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Abstract

Vitiligo is a depigmenting skin disorder of unknown etiology, which presents with nonscaly, chalky-white macules. Selective loss of melanocytes is the characteristic feature of vitiligo. Of the many theories proposed for melanocyte loss, convergence theory, which suggests that the combination of biochemical, environmental, and immunological factors play a role in the pathophysiology of vitiligo, is currently the most accepted theory. Treatment options include topical and systemic immunosuppressants, phototherapy, and surgical techniques. The subtype, extent, distribution, and activity of disease are the determining factors for treatment choice. In this chapter, the pathogenesis, clinical features of vitiligo, and treatment options are discussed.

Keywords: vitiligo, pathogenesis, clinical features, treatment

1. Introduction

Vitiligo is a pigmentation disorder characterized by depigmented macules and patches on the skin. The prevalence of vitiligo ranges from 0.4 to 2.0% worldwide. Vitiligo has no predilection for age, gender, racial background, or skin types [1, 2]. The peak period of onset is between 10–30 years, although it can develop at any age [3–6].

Vitiligo is classified as an autoimmune disease having a genetic basis and an association with environmental factors, including chemical triggers, skin injury, sunburn, and virus infection. Vitiligo is considered to develop as a result of metabolic, oxidative stress, and cell detachment abnormalities [7, 8].

Vitiligo is classified into two major forms: nonsegmental vitiligo (NSV) and segmental vitiligo (SV) [2]. Nonsegmental vitiligo includes acrofacial, mucosal, generalized, universal, mixed, and rare variants. Generalized vitiligo is the most common subtype which often involves the face and acral regions [9].

Vitiligo is a psychologically devastating skin disease, and it is associated with depression, stress, fear, shame, insecurity, sadness, and low self-esteem, which could lead to social isolation or even suicidal ideation [10–13].

Therefore, vitiligo has considerable psychological and social effects on daily life [3].

2. Etiology and pathogenesis

Vitiligo is characterized by the destruction of melanocytes, which leads to pigment loss in the affected areas. The pathogenesis of vitiligo has not yet been fully elucidated. Various theories, including autoimmune theory, adhesion defect theory, biochemical and neural theory, viral theory, intrinsic theory, zinc-α2-glycoprotein deficiency hypothesis and biochemical, and molecular and cellular alterations accounting for the loss of functioning melanocytes in vitiligo have been proposed [14]. Familial aggregation of vitiligo supports the genetic basis of the disease. HLA-associated genes, including HLA-A2, HLA-DR4, and HLA-DR7 alleles [15–17] and non-HLA genes, including DDR1, XBP1, NLRP1, PTPN22, and COMT [18] have been linked to vitiligo susceptibility.

2.1 Autoimmune theory

The autoimmune theory of vitiligo proposes that autoimmune effector mechanisms are involved in melanocyte destruction. The association of vitiligo with several autoimmune diseases, including autoimmune thyroid diseases, alopecia areata, halo nevi, and Addison's disease supports the autoimmune basis of vitiligo [19–23]. Several circulating autoantibodies having a specificity for pigment cells have been detected in sera of vitiligo patients. Antimelanocyte antibodies, especially against tyrosinase one and two (TRP-1 and TRP-2) are found in high levels in about 10% of patients [24–27]. Although the role of antimelanocyte antibodies in vitiligo is still not well known. These autoantibodies are currently considered to develop as a consequence of secondary humoral response to melanocyte destruction [28]. Studies revealing CD4+ and CD8+ lymphocytes in the dermal-epidermal junction of areas of skin near a vitiligo lesion suggest the activation of cell-mediated immunity in vitiligo [29, 30]. Cytotoxic CD8+ T cells, which recognize melanocyte-specific antigens, such as tyrosinase, Melan-A/MART-1, gp100, TRP-1, and TRP-2, have been shown to exert antimelanocytic cytotoxic activity *in vitro* [31, 32]. Elevation of tumor necrosis factor-α (TNF-α), interferon-γ (IFN γ), and IL-10 and IL-17 also have been demonstrated in the blood and tissues of vitiligo patients [33, 34].

2.2 Adhesion defect theory

"Melanocytorrhagy" theory, proposed by Gauthier et al. in 2003 suggests that the major predisposing factor for the development of vitiligo is the primary defective adhesion in the epidermis due to the defective synthesis of extracellular matrix components by keratinocytes and the impaired formation of the basement membrane [35, 36]. This theory argues that chronic detachment and transepidermal loss of melanocytes caused by trauma underlies vitiligo pathogenesis, which is also supported by koebnerization, seen in vitiligo lesions. Overexpression of tenascin in vitiligo patients may play a role in decreasing melanocyte adhesion [37]. Autoantigens released during melanocytorrhagy are hypothesized to cause autoimmune activation provoked by dendritic cells or memory T cells [35, 36].

2.3 Biochemical theory

The biochemical hypothesis argues that biochemical abnormalities of melanocytes and keratinocytes leading to aberrant melanization are involved in vitiligo

pathogenesis. Oxidative stress is implicated in the destruction of melanocytes [37–40]. Defective free radical defense, excessive quantities of hydrogen peroxide (H_2O_2), and the accumulation of toxic intermediate metabolites of melanin synthesis are suggested to play a role in this process [41]. Danger signals named damage-associated molecular patterns (DAMPs), including reactive oxygen species (ROS) and iHSP70, are released from stressed melanocytes [42]. Reactive oxygen species (ROS) lead to the imbalance of prooxidant and antioxidant systems in favor of the prooxidant system. Elevation of oxidative stress markers (superoxide dismutase, malondialdehyde, and ROS) and a reduction of antioxidative enzymes (catalase, glutathione peroxidase, glutathione reductase, thioredoxin reductase, thioredoxin, and superoxide dismutases), and the repair enzymes result with the increased sensitivity of melanocytes to external prooxidant stimuli [37–39]. Defective function of mitochondria, such as alterations in the mitochondrial transmembrane potential and in the electron transport chain, is also suggested to play a role in the pathophysiology of vitiligo [37, 43, 44].

Oxidative stress also affects the recycling of tetrahydrobiopterin, which acts as an essential cofactor in the synthesis of L-tyrosine from L-phenylalanine in tyrosinase synthesis [14]. Tyrosinase is a key enzyme in the formation of melanin [45]. Oxidative stress modifies the active site of dihydropteridin reductase, which plays a role in the recycling process of 6-tetrahydrobiopterin [39]. As a result, the production of hydrogen peroxide increases, and catalase levels decrease, contributing to melanocyte death [46, 47].

2.4 Neural theory

The "neural theory," which was proposed by Lerner's suggests that dysfunction of the sympathetic nervous system (SNS) affects the melanin production and causes depigmentation [48]. The cutaneous blood flow was found approximately three times higher on the segmental vitiligo lesions *than on* normal skin with iontophoresis and laser Doppler flowmetry [49]. Elevated levels of nerve growth factor (NGF), and correlation of HVA and VMA levels with disease activity have been reported in vitiligo patients [50]. Mental stress can also trigger the secretion of catecholamines by stimulating the hypothalamic-pituitary-adrenal axis [51, 52]. Catecholamine discharge induced by stressors leads to vasoconstriction, hypoxia, and overproduction of oxygen radicals that cause melanocyte destruction [51, 52].

2.5 Viral theory

Chronic hepatitis C virus (HCV) infection and autoimmune hepatitis are found strongly associated with vitiligo [53]. A low hepatitis B virus (HBV) seropositivity in vitiligo patients has been reported [54]. Previous or concurrent cytomegalovirus (CMV) infections may play a role in vitiligo onset or deterioration of the disease [55]. Epstein-Barr virus, hepatitis E virus, and the human immunodeficiency virus (HIV) also have been implicated in vitiligo pathogenesis [55–59].

2.6 Zinc-α2-Glycoprotein deficiency hypothesis

The hypothesis that a probable association may exist between Zinc-α2-Glycoprotein (ZAG) deficiency and vitiligo was proposed by Bagherani et al. and Yaghoobi et al. [60, 61]. The ZAG is a 41000 Da adipokine involved in lipolysis, regulation of metabolism,

cell proliferation and differentiation, cell adhesion, and immunoregulation [62, 63]. Zinc-α2-glycoprotein (ZAG) is secreted from keratinocytes and influences melanocyte proliferation, dendricity, and melanin synthesis [64, 65]. Decreased levels of ZAG detected in vitiligo patients support this theory [66].

2.7 Intrinsic theory

The intrinsic theory implies that an intrinsic defect in melanocytes may be the causal factor for melanocyte death. The abnormal rough endoplasmic reticulum, deficiency of melanocyte growth factors, such as basic fibroblast growth factor (bFGF) and decrease in the number of melanocytes, expressing the c-kit receptor in lesional skin may play a role in melanocyte damage [67, 68].

2.8 Apoptosis and accelerated cell senescence

Melanocytes from non-lesional skin of vitiligo patients show some cytologic changes, including cytoplasm vacuolization, DNA marginalization in the nucleus, loss of dendrites, and detachment [67, 69, 70]. In addition, degeneration of basal and suprabasal epidermal cells in the depigmented and normally pigmented skin due to swelling of the membrane-bound organelles, formation of vacuoles, and cytoplasm condensation are among the apoptotic changes [71]. The lower expression levels of the antiapoptotic Bcl-2, FLIP proteins in vitiliginous skin, high levels of the proapoptotic bax, p53 proteins, and of the active forms of caspase-3, 8, and 9 contribute to the apoptotic process in vitiligo [72, 73]. Modification of proliferation and senescence marker expressions (p16, p53, and p21) is another finding reported in vitiligo lesions when compared to keratinocytes from noninvolved skin [73].

2.9 Integrated theory (Convergence theory)

Convergence theory argues that vitiligo may be a syndrome with a multi-factorial etiology rather than a single entity. Since the pathophysiology of vitiligo cannot be sufficiently explained by immune or nonimmune mechanisms, this theory suggesting that the combination of biochemical, environmental, and immunological factors play a role in the pathophysiology of vitiligo is currently the most accepted theory [74].

3. Clinic

The clinical manifestation of vitiligo is chalk-white or milk-white patches with various sizes ranging from a few millimeters to several centimeters. The lesions are generally asymptomatic itching/burning sensation may rarely occur in vitiligo onset [75]. Vitiligo has a chronic, unpredictable course with remissions and exacerbations. The disease is often progressive; spontaneous repigmentation occurs in 10–20% of patients [61].

The term non-segmental vitiligo (NSV) refers to all forms of vitiligo that are not classified as segmental vitiligo (acrofacial, mucosal, generalized, universal, mixed, and rare variants). Segmental vitiligo tends to have an earlier age of onset than NSV [76].

3.1 Non-segmental vitiligo subsets (NSV)

3.1.1 Acrofacial

Acrofacial vitiligo clinically presents as depigmented macules localized on the face, head, and distal extremities. The perioral and periocular regions are preferably involved. Vitiligo lesions in the genital areas are also classified in this group. Progression to generalized or universal vitiligo can be seen during the disease course.

3.1.2 Generalized common vitiligo

Generalized vitiligo is characterized by bilateral, often symmetrical, depigmented macules or patches involving multiple parts of the body. Hands, fingers, and face are the most frequent sites involved at the onset. The areas exposed to pressure, friction, and trauma are often affected [9].

3.1.3 Vitiligo universalis

Vitiligo universalis is the most widespread form of vitiligo that is characterized by the involvement of 80–90% of the body surface. It is generally preceded by generalized vitiligo [7].

3.1.4 Mixed vitiligo

Mixed vitiligo is the concomitant existence of segmental and non-segmental vitiligo. Non-segmental vitiligo is generally preceded by segmental form. The clinical features are: (1) the absence of depigmented areas in a segmental distribution at birth and in the first year of life and exclusion of nevus depigmentosus by Wood lamp examination; (2) NSV development following SV after a period of at least 6 months; (3) SV involving at least 20% of the dermatomal segment or following a definite Blaschko linear distribution; (4) different treatment responses to conventional narrow band ultraviolet B (NB-UVB) between SV (poor response) and NSV (good response). The presence of leukotrichia and halo nevi at onset in patients with SV may be risk factors for developing mixed vitiligo [77].

3.1.5 Mucosal vitiligo

Oral and/or genital mucosae are typically involved. Mucosal vitiligo may be an isolated condition or may occur in the course of generalized vitiligo.

3.1.6 Rare forms

Vitiligo punctata is characterized by 1- to 1.5-mm sized, sharply demarcated depigmented, and punctiform macules affecting any area of the body [78].

Hypochromic vitiligo or vitiligo minor refers to a partial defect in pigmentation resulting from hypopigmented macules. A seborrheic distribution on the face and neck is seen. Hypochromic vitiligo exclusively affects dark-skinned individuals [79].

Follicular vitiligo is characterized by leukotrichia in the absence of depigmentation of the surrounding epidermis [80].

Segmental vitiligo presents with depigmented macules arranged in a segmental pattern that usually does not cross the midline. It is 10 times less common than other vitiligo types. The majority (87%) of the cases are detected before the age of 30 [76, 81]. Involvement of body hair (leukotrichia) and rapid onset are typical. Similar to NSV, the characteristic lesion is a nonscaly, chalky-white, amelanotic macule. In more than 50% of cases, the head is affected with the trigeminal dermatome most commonly involved [82]. The other common localizations are the trunk, limbs, extremities, and neck. In SV, the depigmentation progresses within the segment over a period of 6–24 months. After this period, the SV patch most often remains stable [76]. Segmental vitiligo is more refractory to treatment than other variants, possibly due to its more frequent association with leukotrichia and the deficiency of melanocyte reservoirs, which are involved in the repigmentation process [81].

Unclassifiable forms or undetermined vitiligo include focal vitiligo and mucosal vitiligo.

a. **Focal vitiligo:** Focal vitiligo is characterized by depigmented patches located in a small area without a typical segmental distribution and is classified as an undetermined type of vitiligo. A more definitive diagnosis can be made when the lesions have not evolved into non-segmental or segmental vitiligo after a period of 1–2 years [83].

b. **Mucosal vitiligo:** Involvement of one mucosal site is classified as indeterminate [84].

Vitiligo may show morphological variations, including trichrome, quadri-chrome vitiligo, penta-chrome vitiligo, blue vitiligo, and inflammatory vitiligo.

Trichrome vitiligo is characterized by the presence of an intermediate zone of hypopigmentation located between a vitiligo macule and normal pigmented surrounding skin. Hann et al. suggested that trichrome vitiligo a as a variant of unstable vitiligo [85].

Quadri-chrome vitiligo is characterized by the presence of perifollicular repigmentation in association with trichrome vitiligo [61].

Penta-chrome vitiligo is a rare vitiligo variant that shows blue-gray hyperpigmentation in addition to white, tan, and brown colors [61].

Blue vitiligo: Blue vitiligo is a unique variant of vitiligo presenting with asymptomatic bluish macules histopathologically corresponding to the presence of numerous dermal melanophages and the absence of epidermal melanocytes [86–88]

Inflammatory vitiligo: It is characterized by erythema on the areas of depigmentation and/or the border of the lesion [89]. These changes can be related to aggressive therapy.

3.2 Treatment

Various treatment strategies aiming to inhibit the immune response, reduce melanocyte destruction and reactivate residual melanocytes have been designed for the treatment of vitiligo. Choice of treatment is decided according to the subtype, the extent, distribution, and activity of the disease. The patient's age, phototype, effect on quality of life, and motivation for treatment should be considered in the treatment plan [7]. Treatments can be categorized as pharmacological, surgical, and physical

treatments, which can be also used as a combination. Pharmacological treatments include topical and systemic steroids.

3.3 Pharmacological treatments

3.3.1 Topical treatments

3.3.1.1 Topical corticosteroids

Topical corticosteroids (TCS) are used as first-line treatments as monotherapy in localized vitiligo or in combination with phototherapy or other topical agents in generalized vitiligo. Topical corticosteroids (TCS) have anti-inflammatory and immunomodulating effects. Potent or ultrapotent corticosteroids may be used for the lesions on the body; midpotency topical corticosteroids should be used for the face, neck, intertriginous areas, and the lesions in children. Topical steroids can be used as daily or twice-daily applications in a cyclical fashion with treatment-free intervals (e.g., 1 week on then 1 week off for 6 months or application for 5 consecutive days followed by 2 days off) [90]. The treatment period should not be longer than 3 months because of adverse effects and tachyphylaxis. The advantages of topical steroid treatment therapy include wide availability, low cost, and efficacy. Recurrence after treatment cessation, and cutaneous side effects, such as skin atrophy, telangiectasia, and striae are the factors limiting corticosteroid use.

3.3.1.2 Topical calcineurin inhibitors

Calcineurin inhibitors can be effective in vitiligo treatment by regulating the altered cytokine network. This class of drugs includes tacrolimus and pimecrolimus. Calcineurin inhibitors bind to cytoplasmic protein macrophilin-12, forming a complex that blocks calcineurin. Calcineurin blockage inhibits the proliferation and activation of T cells, and the production of IL-2, IL-3, IL-4, IL-5, IFN-γ, and TNF-α, and suppresses the immune-mediated cutaneous inflammation [91]. Topical tacrolimus also stimulates melanocyte growth resulting in repigmentation [92]. Topical calcineurin inhibitors are generally the treatment of choice for face and neck vitiligo.

Tacrolimus 0.1% ointment was reported to be almost as efficacious as clobetasol propionate 0.05% ointment in a double-blind randomized controlled study [93–95]. Furthermore, a twice-weekly application of 0.1% tacrolimus ointment was shown to prevent the depigmentation of vitiligo patches that showed repigmentation after treatment [96]. Tacrolimus 0.1% ointment plus excimer laser was found to be more effective than placebo plus excimer laser [97].

Selective mode of action and absence of cutaneous atrophy and systemic absorption are some of the advantages of calcineurin inhibitors. No definite relationship between topical calcineurin inhibitor use and malignant tumors has been identified [93, 94, 98]. More studies about the possible risks of cutaneous and extracutaneous cancers are warranted.

3.3.1.3 Topical vitamin D derivatives

Vitamin D is synthesized in the epidermal keratinocytes under UVB light [99]. In addition to its role in regulating calcium and bone metabolism, vitamin D has immunoregulatory properties. The topical application of vitamin D has been shown

to increase the number of L-3,4-dihydroxyphenylalanine-positive melanocytes [100]. Vitamin D analogs (calcipotriol and tacalcitol ointment) act in vitiligo by halting the local autoimmune process and activating melanocytic precursors and melanogenic pathways [101]. Lack of skin atrophy and easy application are the benefits of topical vitamin D derivatives. The use of calcipotriene may fasten the process of repigmentation and reduce overall cumulative exposure during phototherapy but appreciable repigmentation has not been obtained when used alone [81].

3.3.1.4 Pseudocatalase

Pseudocatalase is a complex, which is activated by ultraviolet B (UVB) radiation or natural sun and has been used to replace impaired catalase. Controversial results regarding the efficacy of pseudocatalase in vitiligo have been reported [102–105].

3.3.2 Systemic treatment

3.3.2.1 Systemic corticosteroids

Systemic corticosteroids can be administered as pulse therapy and short periods to stabilize the progression of vitiligo and induce repigmentation at the onset or early stages of the disease [106].

3.4 Physical treatment

3.4.1 Phototherapy

Phototherapy comprises narrowband UVB (NB UVB 311 nm), broadband UVB (BB UVB 290–320 nm), and photochemotherapy**.** UV plays a role in vitiligo treatment by regulating the activity of inflammatory cytokines, reducing the number of Langerhans cells, and polarizing the immune response toward Th2 profile. UV radiation also affects melanogenic cytokines involved in stimulating melanogenesis and the release of epidermal factors that stimulate melanocyte proliferation and migration [107]. Phototherapy shows better results if initiated early in the disease course [108]. It is used as first-line therapy in the treatment of extensive diseases. A combination of phototherapy with topical therapies, such as corticosteroids, tacrolimus, or calcipotriol, is also possible. Phototherapy cannot be used in patients with a history of xeroderma pigmentosum, systemic lupus erythematosus, porphyrias, skin viral infections, and previous treatment with photosensitizing agents. Since UV is a well-known cause of nonmelanoma skin cancers (NMSCs) and melanoma, concerns regarding whether repetitive UV light exposure during long-term phototherapy leads to an increase in the risk of photocarcinogenesis exist. However, in a meta-analysis, UV phototherapy has been reported to be a safe treatment for vitiligo with no significant risk of skin cancer [109].

3.4.2 Ultraviolet B narrowband

Narrowband UV (NB UVB) light (311 +/–2) is an effective and safe treatment modality in moderate or severe generalized vitiligo. In the last decade, NB UVB has become the first-line therapy for extensive progressive vitiligo due to its superiority to PUVA and relatively few side effects. It also has the advantage of being safely used in children during pregnancy or lactation.

Narrowband UV (NB UVB) light has been shown to have a greater response rate and treatment tolerance than PUVA and results in a better color match [110]. The repigmentation rate has been reported between 12.5% and 71.4% in various studies [111, 112]. Many therapeutic protocols are available, but the most commonly used NBUVB protocol is the application of the first dose of irradiation in doses between 0.075 J/cm^2 and 0.25 J/cm^2 and a dose increase by 20% in successive applications [113]. Treatment responsive patients can be treated with NBUVB for a maximum of 24 months. In children, the maximum allowable treatment duration is 12 months [114].

3.4.3 PUVA

Photochemotherapy (PUVA) is a treatment involving an exogenous photosensitizer mainly psoralen, followed by ultraviolet A (UVA) irradiation. UVA (320–400 nm). The mechanism of treatment is based on photoconjugation of psoralens in melanocyte DNA resulting in the proliferation of melanocytes, increased number of melanosomes, and their further transfer to keratinocytes. The psoralen derivative methoxsalen in an oral dose of 0.4 mg/kg body weight is administered 1–2 hours prior to irradiation. After treatment, UVA-blocking glasses and broad-spectrum sunscreens should be used [107]. PUVA is moderately effective in widespread vitiligo [115]. Complete repigmentation occurs in only 15–20% of patients treated with PUVA [115]. For patients with involvement of less than 20%, topical PUVA is indicated. For topical PUVA therapy methoxsalen, 0.1% is applied to vitiligo lesions 30–60 minutes before treatment.

3.4.4 Water bath PUVA

Water bath PUVA is a phototherapy method, in which the patient lies in a bathtub containing psoralen water for 15 min to provide the absorption of the drug on the skin before light therapy. This method is especially beneficial in children for whom oral medicines are not safe [116].

3.5 Laser therapy

The 308-nm excimer laser, formally named as the xenon chloride (XeCl) excimer (excited dimer) laser emits a monochromatic and coherent beam of narrow-band UVB (NbUVB) photons at 308 nm in short pulses focusing on the vitiliginous lesion [107]. These light sources are useful for safely treating small localized vitiligo lesions.

Fewer side effects compared to NBUVB occur since one lesion is treated at a time. Optimal esthetic results with minor contrast between normal and affected skin are obtained [107]. Long targeted treatment with an excimer laser promotes T-cell apoptosis and stimulates melanocyte development and progression along the hair follicle [117]. Two treatment sessions per week are administered for about 6 weeks. Treatment responses with an excimer laser are more rapid than NBUVB. Combination with topical tacrolimus or steroids results in enhanced treatment efficacy. Despite the lack of evidence, it is recommended that phototherapy should be continued for at least 3 months to halt the disease and induce repigmentation. The treatment can be continued for up to 1 year if there is a clinical response. Phototherapy should be stopped when there is no further response [117]. No data for cancer risk and long-term side effects are available, therefore, a cautious use of treatment is recommended.

4. Surgical treatment

Surgical therapies are reserved for patients with stable diseases who have failed to respond to medical treatments. Stable vitiligo is described as the absence of new lesions or an increase in the size of existing depigmented areas for at least 6 months. These treatment methods are typically used for the treatment refractory regions, such as the distal extremities (hands, feet, fingers, toes, palms, soles), elbows, knees, nipples, eyelids, and lips), [118, 119] and better results have been obtained in segmental vitiligo rather than generalized vitiligo [120, 121]. The Koebner phenomenon should be explained to all patients before performing surgical treatments. Several surgical options exist for the transplantation of melanocytes, including miniature punch grafting, suction blister grafting, transfer of noncultured epidermal suspensiosn, and transfer of cultured melanocytes [122]. Combination with UVB therapy results in more favorable treatment outcomes [4].

4.1 Cultured melanocytes

Cultured melanocytes can be transferred as pure-melanocyte suspensions or as melanocyte–keratinocyte co-cultures. Melanocyte–keratinocyte co-cultures have the advantage of containing melanogenic factors released by keratinocytes, which regulate melanocyte growth and differentiation. An autologous melanocyte culture is an effective tool in the treatment of vitiligo. Excellent repigmentation is achieved in 41% to 52% of patients and a good response in 7% to 19% [123, 124]. Several factors, including donor site selection and temperature of the donor tissue, are associated with an increase in the likelihood of successful melanocyte culturing [123]. Donor specimens can be harvested by biopsy or suction/cryo-induced blister method. Preparation of the recipient site can be performed by dermabrasion, suction/cryo-induced blister method Er:YAG laser or CO_2 laser. One of the most effective donor sites is the forearm because it has been found to produce melanocytes that proliferate fastest when cultured [122]. The major advantage of autologous melanocyte culture is its ability to treat a large vitiliginous area using tissue from only a small donor site [124].

4.2 Noncultured epidermal suspensions

In this technique, noncultured melanocyte/keratinocyte suspensions, which are prepared by 0.25% trypsin digestion of a thin piece of donor skin, are grafted to the recipient area. The procedure is performed by injecting the suspensions into blisters raised with liquid nitrogen or seeded onto dermabraded vitiligo lesions [107].

4.3 Minigrafting

Mini-punch grafting is the most commonly used technique for vitiligo repigmentation. With this technique, 2- to 4-mm punch grafts are harvested from a normally pigmented donor site of similar thickness [125, 126]. Generally, the grafts are harvested from the gluteus region or extensor surface of the thigh ("bikini area") [119]. Multiple punch biopsies that are the same size or 0.25 to 0.5 mm smaller than those taken from the donor site are taken from the recipient site [121]. The epidermis of the recipient site is often removed with phototherapy, dermabrasion, cryotherapy, or laser irradiation before the procedure [126]. The grafted area is covered with a

petrolatum gauze dressing or a transparent adhesive tape and fixed with bandages for at least one week. Minigrafting method can also be used to treat difficult areas, such as lips. A cobblestoning appearance is a potential adverse effect of this method [125, 127]. The risk of cobblestoning appearance increases with the increasing size of the punch biopsies.

4.4 Suction blister grafting

Epidermal suction blister grafting is another useful tool available in the surgical management of vitiligo. In this technique, the formation of multiple epidermal blisters is promoted by a negative pressure apparatus which is applied to the normally pigmented donor site, producing 300 to 500 mmHg of pressure [128, 129]. Suction blisters can be simply produced by using the evacuated barrel of a syringe, which can generate negative pressure [130].

Pretreatment of the donor site with PUVA may increase the number of melanocytes available for transplantation [129]. The recipient site is prepared by removing the epidermis through induction of suction blisters, application of liquid nitrogen, PUVA, carbon dioxide laser, yttrium aluminum garnet laser, or dermabrasion. The roofs of the suction blisters formed at the donor site are subsequently removed and transferred to the newly prepared recipient site. The recipient site should be covered with a pressure bandage for 1 week, and the application of an antibiotic ointment at both sites is recommended.

4.5 Split thickness skin grafting

Grafts of the epidermis together with a part of the upper papillary dermis are implanted onto the recipient site. The grafts are harvested most commonly from the gluteal region or thigh. The procedure is performed by grafting of donor skin with a thickness of 0.1–0.2 mm using a hand dermatome or shaving blade fixed in a straight hemostat [129]. The grafts are implanted in recipient areas that have been prepared by dermabrasion or laser ablation. This technique is not suitable for vitiliginous lesions on the palms, soles, and skin folds.

4.6 Micropigmentation

Micropigmentation, also termed medical tattooing, can be a useful alternative treatment for treatment-resistant vitiligo. This technique is performed by the injection of pigment particles into the dermis, manually or with electrically driven needles [131, 132]. Tattooing is useful for sites with a poor rate of repigmentation, such as the lips, nipples, and distal fingers [131, 132].

4.7 Depigmentation

Depigmentation therapy is performed by the application of monobenzyl ether of hydroquinone (MBEH) to normally pigmented skin to induce selective melanocyte destruction. The exact mechanism of MBEH is not clearly known but it has been suggested that MBEH may act by the induction of necrotic changes in melanocyte plasma and nuclear membranes [133]. Typically, MBEH is applied twice daily for 6 to 18 months. A patch test should be performed to detect contact sensitivity to MBEH before treatment.

Depigmentation therapy is reserved for patients with the extensive or recalcitrant disease. Though there is no consensus regarding the stage of the disease that depigmentation should be initiated, it is usually offered for cases with involvement greater than 60% of body surface area or if visible areas, such as the face and hands, are affected [134].

The depigmentation therapy poses a permanent risk of acquiring sunburn. Patients should therefore be advised to minimize sun exposure and apply broad-spectrum sunscreens because of the possibility of the pigment relapse within a few weeks of treatment cessation on sun-exposed sites [135].

The possibility of carcinogenesis from hydroquinones is a debatable issue and the risk of carcinogenesis related to MBEH cannot be excluded [136].

4.8 Camouflage

The use of cosmetic camouflage on the face and other exposed areas can improve the quality of life for patients with vitiligo. Camouflage methods include cosmetic tattoos, dihydroxyacetone, general cosmetics, and various topical camouflage agents [137].

4.9 Novel treatments

4.9.1 Photodynamic therapy

The mechanism of photodynamic therapy (PDT) in vitiligo is based on the fundamental oxidative response. There are controversial results regarding the effect of PDT on vitiligo [138, 139]. Poor treatment responses may be related to the fact that melanin reflects this light length and PDT acts on oxidative stress, which is only one of the several mechanisms involved in the pathogenesis of vitiligo [139].

4.9.2 JAK inhibitors

JAK inhibitors have been offered as a novel treatment option for vitiligo. JAK inhibitors target the JAK/STAT pathway. JAK is involved in IFN-γ secretion. IFN-γ plays a key role in the pathogenesis of the disease and induces genes, including the T-cell chemokine receptor (CXCR3) and its multiple ligands, CXCL9, CXCL10, and CXCL11, which are upregulated in depigmented skin lesions. Activator of transcription (STAT)-1 signaling pathway leads to further recruitment of CXCR3+ CD8+ T cells, which causes melanocyte detachment and apoptosis [140].

JAK inhibitors, including ruxolitinib, baricitinib, and tofacitinib, have been found to be effective in vitiligo, and increasing treatment response is obtained with concomitant UV exposure. However, more studies regarding the ideal dosage of these drugs are required [140, 141]

4.9.3 Non-traditional treatments

Non-traditional treatments may be considered as an alternative for patients unresponsive to standard treatments. Vitamins, nutritional supplements, immunomodulators, khellin, topical and systemic phenylalanine, and herbal products are the most widely used [107]. Herbal formulations contain Psoralea corylifolia, black cumin, barberry root, and P leucotomos. Herbal products have anti-oxidative, anti-stress, immunoregulatory, and skin sensitizating effect to sunlight [116].

5. Conclusion

The etiopathogenesis of vitiligo has not been fully elucidated, despite the new discoveries in recent years. Integrated theory (Convergence theory) is currently the most accepted theory. No treatment option providing a definitive cure for vitiligo exists. Novel treatment modalities, such as JAK inhibitors and photodynamic therapy, enhanced the treatment perspective, while the results of these treatments need to be investigated by further studies.

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Conflict of interest statement

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