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Overview on vitiligo and its treatment

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Abstract

Vitiligo, is a skin disorder, in which the skin loses its pigment due to the loss of melanocytes. The exact cause is still under research but the disorder is linked to autoimmune disease, oxidative stress, genetics and environmental variables. The disease being progressive in nature often spreads all over the body. Globally, Vitiligo affects nearly about 0.5% to 1% of people. In 2012, the most recent and approved classification for Vitiligo was given at Vitiligo Global Issues Consensus Conference (VGICC). Understanding the biological mediators and molecular mechanisms that result in metabolic problems, melanocyte degradation, and autoimmunity is crucial in order to identify innovative therapy targets and drugs that may be able to stop the progression of the condition or even cure vitiligo. Treatment options range from oral antibiotics, topical immunosuppressants, melanocyte promoters, oral immunosuppressants, JAK kinase inhibitors, physical therapy, to surgical intervention. Systemic biological therapies that target cytokines have shown promising results in the treatment of diseases like vitiligo and psoriasis.

Keywords: Vitiligo; Melanin; Autoimmunity; JAK kinase inhibitor; Phototherapy

1. Introduction

Vitiligo is, depigmenting skin disorder, in which there is selective loss of melanocytes (cells imparting color to the skin). As the disorder is progressive in nature, it can spread throughout the body. The exact cause of the disorder is still unknown. Significant recent advancements in the pathophysiology of vitiligo have recognized vitiligo as an autoimmune disease and are linked to problems in metabolism, oxidative stress, and cell detachment as well as genetic and environmental variables [1,2]. The effects of vitiligo can be psychologically distressing and frequently have a significant burden on everyday life, thus it should not be ignored as a cosmetic or unimportant disease [3]. The skin can lose its color by basic mechanism [4]. Melanocytes synthesize melanin within melanosomes which are then transferred to the vicinity of keratinocytes. In the stratum corneum, where they are desquamated into the environment, the keratinocytes transfer the melanin and melanosomes from the basal layer of the epidermis [5]. The skin becomes hypopigmented as a result of some diseases that prevent or slow down the generation of melanin [4]. These conditions include nevus depigmentosus, pityriasis Alba, tinea versicolor, and oculocutaneous albinism.

2. Epidemiology

The most common pigmentary disorder, vitiligo, affects 0.5% to 1% of people worldwide. According to reports, Mexico and Japan have the highest occurrence rates, followed by India [6]. Although vitiligo can appear at any age, around half of cases appear before the age of 20, and about 70% to 80% appear before the age of 30 [7]. According to research, prevalence rises with aging [8]. With an average frequency of 0.25%-2.5%, India has a wide range of prevalence, ranging from 0.46% to as high as 8.8%. Gujarat and Rajasthan have seen the highest rates of prevalence. Vitiligo prevalence ranged from 0.47% in the rural population to 1.78% in the urban population in a sizable study carried out in Surat [9].

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A research in Uttarakhand indicated that the frequency was 2.64% [10]. The sociocultural effects of the disease and the varied ethnic origins in each place are likely to be to blame for this regional diversity [11]. In 7% to 36% of cases, a favorable family history is observed. A first-degree relative is affected in at least 20% of the cases, supporting the idea that hereditary factors play a role in pathogenesis. First-degree relatives including parents, siblings, and children have a 7- to 10-fold increased risk of developing vitiligo [12]. Worldwide vitiligo occurs without any discernible racial or geographic variance. However, groups with darker skin types have higher incidence rates, which may be related to a greater color contrast and related social stigma, which causes these patients to typically present early in the progression of the disease. It has also been discovered to have connections to other autoimmune illnesses and endocrine conditions as thyroiditis and diabetes [13]. Males and females are equally impacted, albeit women and girls seek consultation more frequently, possibly due to the larger negative social impact than men and boys [14,15].

3. Classification of vitiligo

In 2010, Taieb and Picardo divided vitiligo into four basic categories: nonsegmental vitiligo (NSV), segmental vitiligo (SV), and unclassified [16]. The most recent and approved classification of vitiligo was given in 2012 at the Vitiligo Global Issues Consensus Conference (VGICC) based on this classification as shown in figure 1. They divided vitiligo into three main categories: nonsegmental, segmental, and unclassified/undetermined [2].

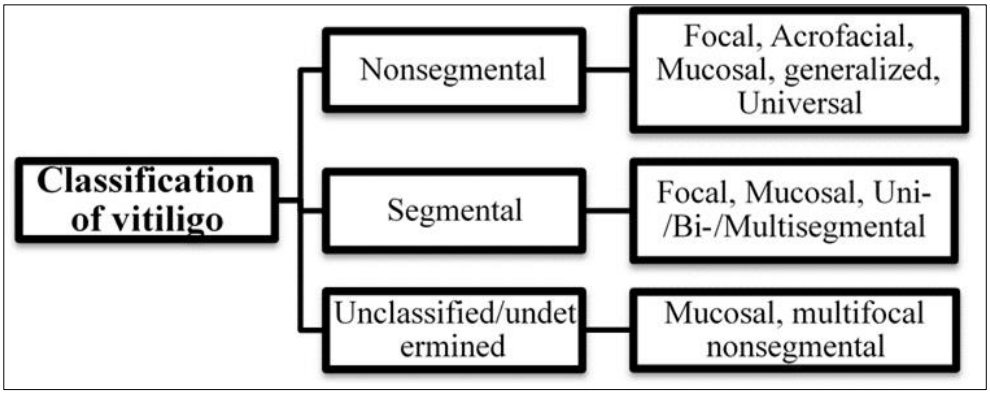

Figure 1 Classification of Vitiligo

3.1 Nonsegmental vitiligo

Depigmented macules that range in size from a few to several centimeters in diameter are the defining feature of non-segmental vitiligo. The macules often have a symmetrical distribution and can be found on both sides of the body. Compared to segmental vitiligo, non-segmental vitiligo is less likely to involve body hair [17]. Nonsegemental Vitiligo further includes the following variants:

3.1.1. Focal

The term "focal vitiligo" refers to a phenotype where there are just one or a few white maculae that are limited to a single anatomical location and lack any visible segmental or zosteriform distribution [17].

3.1.2. Acrofacial

Depigmentation of the distal regions of the extremities (hands rather than feet) and of the facial orifices, the latter in a circular pattern, are included in acrofacial vitiligo as shown in figure 2 [18].

3.1.3. Mucosal

Mucosal vitiligo is characterized by vitiligo on the mouth and mucous membranes, including the genitalia [2].

3.1.4. Generalized/Universal

The body is covered in many depigmented patches and macules. The cheeks, hands, and fingers are typically the first places where depigmentation appears, but it can affect any region of the body [17].

Figure 2 Acrofacial vitiligo

3.2. Segmental Vitiligo

Depigmented macules that are limited to one or more body segments is the feature of segmental vitiligo. These lesions never cross the midline. Involvement of body hair is more common with segmental vitiligo than with nonsegmental Vitiligo. Segmental vitiligo develops quickly and progresses; however, this only lasts for 6–24 months, after which additional development is infrequently observed. Depending on the number of lesions, segmental vitiligo can be uni-, bi-, or plurisegmental [2,17].

3.3. Unclassified/Undetermined vitiligo

This comprises two types of vitiligo that fall outside of the categories of segmental and non-segmental vitiligo which is as follows:

3.3.1. Multifocal vitiligo

One or more macules may be seen in multiple areas of focal vitiligo, which does not have a segmental or zosteriform distribution [2].

3.3.2. Mucosal vitiligo

Involves isolated oral or vaginal mucosae without cutaneous involvement [17].

4. Basic science of Melanin

The color of the skin, hair, eyes, and skin appendages is primarily determined by melanin. It is essential in protecting skin cells from UV exposure. Melanin is produced by the melanosome, a cytoplasmic vesicle similar to the lysosome. Melanosomes are spherical or elliptical organelles that contain cofactors and melanogenic enzymes. During the process of melanogenesis, the pigments eumelanin, which is brown or black, and pheomelanin, which is yellow or red, are both produced. Tyrosinase (Tyr), an enzyme, is crucial for the initial stages of melanin formation. It produces L- 3,4-dihydroxyphenylalanine (l- dopa) by hydroxylating L- tyrosine. L- dopa is subsequently oxidised to make L-dopaquinone, which spontaneously to produce eumelanin. Dopaquinone and cysteine are used to make pheomelanin as shown in Figure 2. The overall color of the appendages and skin is determined by the balance of these two forms of pigment [19]. Skin pigmentation depends on the movement of melanosomes within melanocytes from the site of synthesis near the cell's centre to the cell's periphery before they are transferred to keratinocytes [20-23].

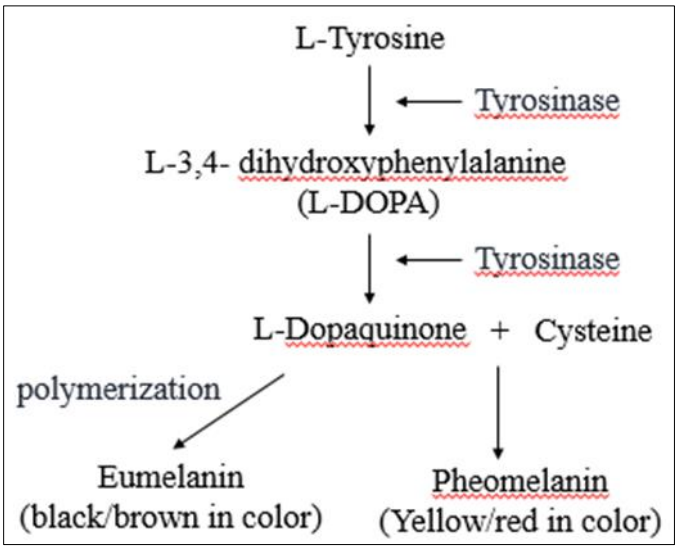

Figure 3 Biosynthesis of melanin

5. Pathophysiology/ Pathogenesis

The absence of functioning melanocytes is a primary feature of the multifactorial disease vitiligo [2]. Multiple pathways have been hypothesized for melanocyte destruction in Vitiligo. Metabolic problems, oxidative stress, production of inflammatory mediators, cell detachment, and autoimmune responses are just a few of the pathways that could be responsible for this loss [24]. The immune system's innate and adaptive arms appear to be engaged. Multiple mechanisms, including immunological attack or cell aging and detachment, could play in the gradual loss of melanocytes. According to the "convergence theory" or "integrated theory," several mechanisms may cooperate in vitiligo to contribute to the degeneration of melanocytes, ultimately producing the same clinical outcome [25,26].

5.1.1. Oxidative stress

In melanocytes, oxidative stress causes local inflammation and the activation of innate immune systems, which in people with a hereditary propensity for developing autoimmunity, results in the production of melanocyte-specific cytotoxic immune responses [27]. According to studies on vitiligo pathogenesis, melanocyte loss may start as a result of oxidative stress [28-31]. In fact, it has been discovered that melanocytes from vitiligo patients are more sensitive to oxidative stress than those from unaffected people and are more challenging to culture ex vivo than those from healthy controls [32]. Melanocytes respond to stress by releasing reactive oxygen species (ROS). According to studies, oxidative stress is the main factor that leads to immunological dysfunction in people who are genetically predisposed to it. Melanocyte death is mediated by activated cytotoxic CD8+ T cells and the chemokine CXCL10 that is produced by interferon-gamma [33,34]. For instance, melanocytes from perilesional vitiligo skin exhibit anomalies in their mitochondria and melanosome structure, as well as a dilated endoplasmic reticulum (ER), all of which are signs of increased cellular stress [35].

5.1.2. Genetics

The role of genetic impacts in the vitiligo development is strongly supported by evidence from numerous research, even though it is obvious that these influences are complex. According to epidemiological research, vitiligo tends to run in families [36]. Several genome-wide association studies (GWAS) have discovered risk alleles that affect the vitiligo development. Tyrosinase, melanocortin 1 receptor, and OCA2 are melanocyte-specific alleles. Stress-related genes (XBP1), genes involved with innate immunity (NLRP1, TICAM1, IFIH1, etc.), and genes linked with adaptive immunity (HLA-A, GZMB, IL2RA, and others) are also risk variations. The TYR gene produces the enzyme tyrosinase, which catalyses the rate-limiting steps of melanin production [37]. A significant autoantigen in generalised vitiligo is tyrosinase [38,39]. A susceptibility variation for nonsegmental vitiligo in TYR that is uncommonly found in melanoma patients has been identified in European white individuals by a genome-wide association study [40]. Vitiligo and melanoma susceptibility appear to be mutually exclusive, pointing to a genetic dysregulation of the immune system's defences against the melanocytic system [37,40].

5.1.3. Environmental Factors

The complex condition of vitiligo is influenced by a number of factors. Although the precise pathophysiology is unclear, it has been suggested that environmental factors may have a significant impact on vitiligo development in genetically susceptible people. In genetically vulnerable individuals, whose melanocytes are more delicate than normal, a precipitating factor could more easily trigger cellular death [41]. Sunburn, pregnancy, stress, and exposure to cytotoxic substances are among the triggering factors that are involved. All of these precipitating elements have the capacity to increase melanin synthesis. According to the study, sunburn (28.8%), mechanical causes (19.2%), chemical variables (16.4%), and emotional stress (55.4%) were the most common precipitating factors [42]. Several environmental contaminants reportedly exhibited selective toxicity to melanocytes both in vitro and in vivo, according to some scientists [43]. The majority of toxins are phenol and catechol derivatives, which are ingredients in bleaching creams. Only a few exposed people, though, experienced hypopigmentation. In addition, it has been claimed that sulfhydryls, systemic medications, mercurials, and arsenic cause vitiligo. People who deal with rubber and industrial oils containing numerous compounds, such as phenolic antioxidants, phenolic germicidal detergents, and para-tertiary-butylphenol, have been reported to develop a contact/occupational vitiligo [44].

5.1.4. Autoimmunity

Vitiligo is caused by the interaction of autoimmune systems with a number of additional variables, such as heredity, the environment, and oxidative stress [35]. Multiple pathways may be used by stressed melanocytes to trigger immunological responses. The autoimmune disorders autoimmune thyroiditis and type 1 diabetes mellitus, as well as vitiligo, are all characterized by cellular stress, innate immunity, and adaptive T cell responses. The existence of antibodies against melanocytes, the relationship with polymorphisms at immune loci, the presence of significant T cell perilesional infiltrates and cytokine production, and the association with other autoimmune illnesses all suggest the role of autoimmunity in vitiligo [36].

Innate Immunity

Oxidative stress and adaptive immunity in vitiligo are connected by innate immunity. Early in the course of vitiligo, it is likely that innate immune cells get activated by detecting exogenously or endogenously produced stress signals emitted from melanocytes and perhaps keratinocytes [45,46]. Recent research has found evidence of innate immune activation in the skin of vitiligo victims, which may be the cause of the disease's onset. Natural killer (NK) cells, which are crucial parts of innate immunity and aid in the control of viral infection and tumor growth. They have the ability to secrete cytokines like interferon-gamma (IFN-γ), which can directly kill target cells. One study found that NK cells infiltrated both the lesional and non-lesional skin of vitiligo patients, indicating that they may be the disease's early initiators via spotting melanocyte stress. If NK cells in a patient's skin get activated, they may turn cytotoxic and directly harm or eliminate melanocytes, or they may alternatively generate cytokines like IFN-γ to encourage the infiltration of T cells, which then cause depigmentation. It will take more research to ascertain the part that NK cells play in the development of vitiligo and whether or not concentrating therapy efforts on this population would be successful [13].

Adaptive Immunity

Melanocyte-specific cytotoxic CD8+ T cells that move into the skin, locate their melanocyte targets, and kill them are the main effector cells in vitiligo. This was first determined from the CD8+ T lymphocytes that were present in the lesional epidermis and their close proximity to dying melanocytes [47]. When lesional skin was removed from vitiligo patients and the invading T cells were separated and grown, their functional involvement in promoting depigmentation was made clear. Both CD4+ and CD8+ T cells were present in these cells, and a significant portion of the CD8+ T cells were melanocyte-specific and capable of in vitro melanocyte apoptosis. The mixed T-cell populations moved into the skin, located the melanocytes, and caused apoptosis when they were cultured with non-lesional skin from the same patient. Purified CD8+ T cells were considerably more effective in killing melanocytes than CD8-depleted T cells [48]. According to these research, CD8+ T lymphocytes are both necessary and sufficient to kill melanocytes in situ. IFN-γ, which is necessary for depigmentation, was discovered to be produced by lesional CD8+ T cells [49,50]. It was also shown that the IFN-γ induced chemokine CXCL10 was necessary for the development and maintenance of vitiligo's depigmentation. In fact, inhibiting CXCL10 with a neutralizing antibody prevented and reversed vitiligo, demonstrating the viability of this approach as a potential therapeutic approach [51].

6. Treatments

Current treatments, including topical immunosuppressant's, phototherapy and surgical approaches, partially address these goals in overall non-targeted ways. Some have suggested that stabilizing melanocyte stress by administering

antioxidants either topically or orally may improve current treatments, though they have not yet been proven highly effective.

6.1.1. Antioxidants

Oral antioxidants, including vitamins and herbal supplements, have also been suggested as adjuvants to conventional therapy, but further research is required to confirm their efficacy [52]. As an illustration, the oral antibiotic minocycline was investigated as a potential treatment for vitiligo after in vitro research revealed that it shields melanocytes from oxidative stress and inhibits their loss in the early stages of the condition [53]. Topical antioxidants with powerful anti-inflammatory, antioxidant, and anti-apoptotic activities include capsaicin and curcumin, which are derived from chilli pepper and turmeric, respectively. By restoring mitochondrial permeability and mitochondrial membrane potential and inhibiting the intrinsic apoptotic pathway, respectively, capsaicin and curcumin pretreatment of perilesional vitiligo skin of patients showed a beneficial effect in preventing mitochondrial damage and apoptosis in the keratinocytes from perilesional vitiligo skin [54]. However, dietary curcumin was found to contribute to oxidative stress in acute vitiligo and impede repigmentation in a trial in which Asian individuals with the condition regularly ingested turmeric [55].

6.1.2. Topical Immunosuppresants

Mycophenolate mofetil, a topical immunosuppressant, targets the immune dysregulation in vitiligo by causing activated lymphocytes to die, reducing the number of monocytes and CD4 and CD8 lymphocytes at the sites of inflammation, and inhibiting the production of antibodies by B cells. These actions reduce hypopigmentation. [56]. The antimitotic activity of 5-fluorouracil causes the adverse effect of hyperpigmentation [57]. Repigmentation was the consequence of topical 5-FU administration following cutaneous abrasion [58]. The inhibitor cells or elements in the dermis or epidermis that are harmful for melanocytes are likewise negatively impacted by 5-FU [59,60].

6.1.3. Melanocyte Proliferators

Afamelanotide, a strong and long-lasting synthetic -MSH analogue, may be an effective vitiligo treatment. By attaching to the melanocortin-1 receptor (MC1R), it activates the main melanogenesis pathway, enhances pigmentation, and boosts melanocyte proliferation. Afamelanotide produces strong tanning, which is quite concerning in those with fair skin because it produces a stark color contrast. As a result, those with dark complexion saw the best effects [61,62].

In both human and animal research, prostaglandin F2 alpha (PGF2) analogues have been shown to be effective treatment choices for vitiligo, with greater efficacy when paired with phototherapy or topical steroids. Instead of having a direct impact on melanogenesis, the therapeutic effectiveness is mediated indirectly by the activation of COX-2 and PGE2. The PGF2 analogues being researched in separate studies are latanoprost (0.005%), bimatoprost (0.03%), and travoprost (0.004%) ocular solutions [63,64].

Analogs of prostaglandin E2 (PGE2), due to their role in immunomodulation, melanogenesis, melanocyte proliferation, and maturation, prostaglandins are beneficial in treating vitiligo. PGE2 synthesis has increased, which is why ultraviolet radiation's (UVR) ability to treat vitiligo by causing repigmentation is effective. Keratinocytes produce PGE2 as a result of the mitogenic and inflammatory stimuli that UVR produces in the cyclooxygenase 2 enzyme. Research on vitiligo patients have shown considerable repigmentation with the slight adverse effect of transitory burning sensation when applied twice daily for 6 months. Animal studies showed enhanced melanocyte density on topical treatment of PGE2 gels. [65]

6.1.4. Oral Immunosuppressants

Azathioprine is a common immunosuppressive medication for autoimmune diseases. It is only occasionally used in vitiligo. The effectiveness of it has been tested in combination with oral PUVA therapy and compared to oral PUVA therapy alone. The dosage of azathioprine administered was 0.6-0.75 mg/kg (max dose 50 mg per dose). In the azathioprine and PUVA therapy combination group, body surface repigmentation was observed after a 4-month follow-up at 58.4%, compared to 28.4% in the PUVA therapy alone group. The azathioprine-only group repigmented the acral areas more effectively, but the azathioprine and PUVA combination group repigmented the perifollicular areas more quickly. Two patients who were on azathioprine experienced stomach distress. Only this side effect was noticed [66].

6.1.5. JAK kinase inhibitors

A patient with progressing widespread vitiligo experienced significant repigmentation after using the JAK1/3 inhibitor oral tofacitinib citrate, which the FDA has licensed for use in treating moderate-to-severe rheumatoid arthritis [67]. In a patient with coexisting vitiligo, roxolitinib, a JAK1/2 inhibitor authorized for the treatment of myelofibrosis and

polycythemia vera, was also found to be beneficial [68]. On July 18 in the year 2022, FDA approved ruxolitinib (Opzelura) cream 1.5 percent as a treatment for the most common form of vitiligo.

6.1.6. Physical Therapy

Phototherapy

The mechanism of action of nb-UVB phototherapy, which uses ultraviolet radiation with a wavelength of 311 nm, involves immunosuppression, induction of melanocyte differentiation, synthesis of melanin, and migration of melanocytes from perilesional skin [69]. By suppressing the immune system and fostering an environment that is conducive to the formation of melanocytes, PUVA radiation (wavelength of 320-340 nm) causes melanogenesis [70]. Laser treatment EL Targeted phototherapy is made possible using excimer light, which has a wavelength of 308 nm. This light has a direct cytotoxic effect on T cells and stimulates melanocyte migration [71].

6.1.7. Surgical Treatments

When vitiligo is stable, surgery is recommended; however, when severely depigmented areas are resistant to medical therapy, surgery is not always an option [72]. Blister roof grafting [73,74], punch grafting followed by psoralen plus ultraviolet A (PUVA) [75], melanocyte culture and transplantation [76,77], split skin grafting [78], and dermabrasion [79] are all surgical treatments used to treat the condition.

7. Conclusion

A common multifactorial skin condition with a very complicated pathophysiology is vitiligo. The cause and pathogenesis of vitiligo remain unknown, despite recent significant advancements in our understanding of the condition. There are still questions concerning what ultimately leads to the degeneration of melanocytes, and further research is required to fully understand the etiology of vitiligo. To find novel treatment targets and medications that could arrest the evolution of the disease or possibly cure vitiligo, it is critical to understand the biological mediators and molecular mechanisms that result in metabolic abnormalities, melanocyte degeneration, and autoimmune. It has been proven that cytokine-targeting systemic biological treatments can be effective in treating conditions like psoriasis and vitiligo.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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