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A REVIEW ON LEUCODERMA (VITILIGO)

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ABSTRACT

Vitiligo, a common depimenting skin disorder, has an estimated prevalence of 0.5–2% of the population worldwide. The disease is characterized by the selective loss of melanocytes which results in typical nonscaly, chalky-white macules .In recent years; considerable progress has been made in our understanding of the pathogenesis of vitiligo which is now clearly classified as an autoimmune disease. Vitiligo is often dismissed as a cosmetic problem, although its effects can be psychologically devastating, often with a considerable burden on daily life. In 2011, an international consensus classified segmental vitiligo separately from all other forms of vitiligo, and the term vitiligo was defined to designate all forms of nonsegmental vitiligo. This review summarizes the current knowledge on vitiligo and attempts to give an overview of the future in vitiligo treatment.

Key Words: Vitiligo, skin disorder, melanocytes, autoimmune disease, segmental vitiligo, mnonsegmental vitiligo, treatment.

1. Introduction

Vitiligo, a depigmenting skin disorder, is characterized by the selective loss of melanocytes, which in turn leads to pigment dilution in the affected areas of the skin. The characteristic lesion is a totally amelanotic, nonscaly, chalky-white macule with distinct margins. Considerable recent progress has been made in our understanding of the pathogenesis of vitiligo, and it is now clearly classified as autoimmune disease, associated with genetic and environmental factors together with metabolic, oxidative stress and cell detachment abnormalities [1, 2]. Vitiligo should not be dismissed as a cosmetic or insignificant disease, as its effects can be psychologically devastating, often with a considerable burden on daily life [3].

The extent and rate of color loss from vitiligo is unpredictable and have sharp margins. The hair from the skin also becomes white. The inside of the mouth and nose may also be involved. It occurs in people with all skin types and color but mostly occurs in people with dark skin where all the areas of their body are dark and effected areas are white in color. This condition even causes much psychological stress to the effected people from relatives and society.This may result in many other diseases to attack these individuals. It is very easy to diagnose this disease as it can be directly done by the physical examination. Descriptions of a disease believed to be vitiligo date back to a passage in the medical text Ebers Papyrus circa 1500 BCE in ancient Egypt. Mentions of whitening of the skin were also present circa 1400 BCE in sacred Indian texts such as Atharvaveda as well as Shinto prayers in East Asia circa 1200 BCE. The Hebrew word "Tzaraath" from the Old Testament book of Leviticus dating to 1280 BCE (or 1312 BCE]) described a group of skin diseases associated with white spots.

The name "vitiligo" was 1st employed by the Roman MD Aulus Cornelius Celsus in his classic medical text de Medicina. The etymology of the term "vitiligo" is believed to be derived from "vitium", which means "defect" or "blemish". [4]

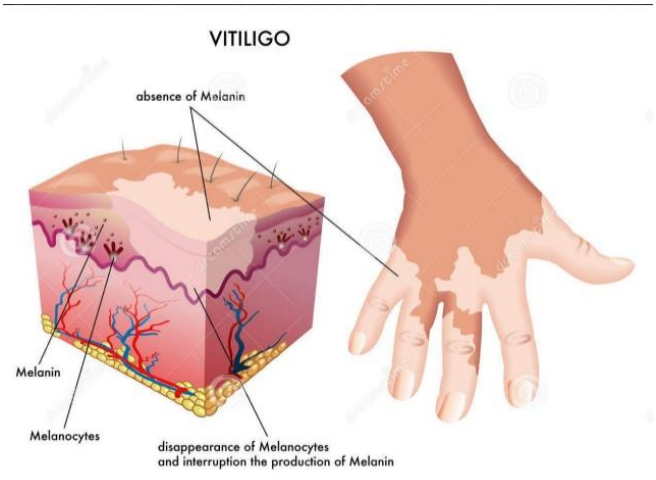

Fig. 1 Anatomy of skin depigmentation

2. Epidemiology

Vitiligo is the most common depigmenting skin disorder, with an estimated prevalence of 0.5–2% of the population in both adults and children worldwide. One of the earliest and largest epidemiological surveys to have been reported was performed on the Isle of Bornholm, Denmark, in 1977, where vitiligo was reported to affect 0.38% of the population. Vitiligo affects ethnic groups and people of all skin types with no predilection. However, there seem to be large geographic differences. For example, a study in the Shaanxi Province of China reported prevalence as low as 0.093%, whereas regions of India had rates as high as 8.8%. This high value could be due to the inclusion of cases with chemical and toxic depigmentation, or because these data might reflect the prevalence of a single skin institute in Delhi. Moreover, the disparity in the prevalence data may be due to higher reporting of data in places where social and cultural stigma are common, or where lesions are more evident in darker-skinned individuals. An extensive in-depth review of prevalence data from more than 50 worldwide studies has demonstrated that the prevalence of vitiligo ranges from a low of 0.06% to a high of 2.28%. A meta-analysis assessing the prevalence of vitiligo which included a total of 103 studies found that the pooled prevalence of vitiligo from 82 population- or community-based studies was 0.2% and from 22 hospitalbased studies 1.8%. SV accounts for 5–16% of overall vitiligo cases; however, its incidence and prevalence are not well established. The prevalence of SV ranges from 5 to 30% in published reports. This variability in epidemiological data could be accounted for by differences in disease classification due to the lack of consensus in previous years, inconsistent reporting by patients and varied populations [6].

Males and females are equally affected, although women and girls often seek consultation more frequently, possibly due to the greater negative social impact than for men and boys. NSV develops at all ages but usually occurs in young people between the ages of 10 and 30 years. Twenty-five percent of vitiligo patients develop the disease before the age of 10 years; almost half of patients with vitiligo develop the disease before the age of 20 years and nearly 70–80% before the age of 30 years. Most populations have mixed age-of-onset groups and double peaks as has been noted. SV tends to occur at a younger age than NSV: before the age of 30 years in 87% of cases and before the age of 10 years in 41.3%. In the report of Hann and Lee [5], the mean age of onset was 15.6 years. The earliest reported onset was immediately after birth, whereas the latest was 54 years. Most cases were less than 3 years in duration at referral, ranging from 2 months to 15 years [6].

3. Etiology

The exact etiology of vitiligo is unknown. It is frequently associated with multiple autoimmune diseases. There are various theories about its pathogenesis and the etiology is multifactorial. It is characterized by incomplete penetrance, genetic heterogeneity, and multiple susceptibility loci. Family and other twin studies have shown that inheritance is complex and also involves both environmental and genetic factors. Additionally, it is hypothesized that genetic factors can

influence the age of onset of vitiligo. The inheritance of vitiligo may also include genes associated with the biosynthesis of melanin, regulation of autoantibodies, and response to oxidative stress [7].

Recent research studies have not highlighted any associations with any certain HLA type. There is a strong reason to believe that segmental and nonsegmental vitiligo has a unique genetic mechanism, which can account for variable treatment responses [8].

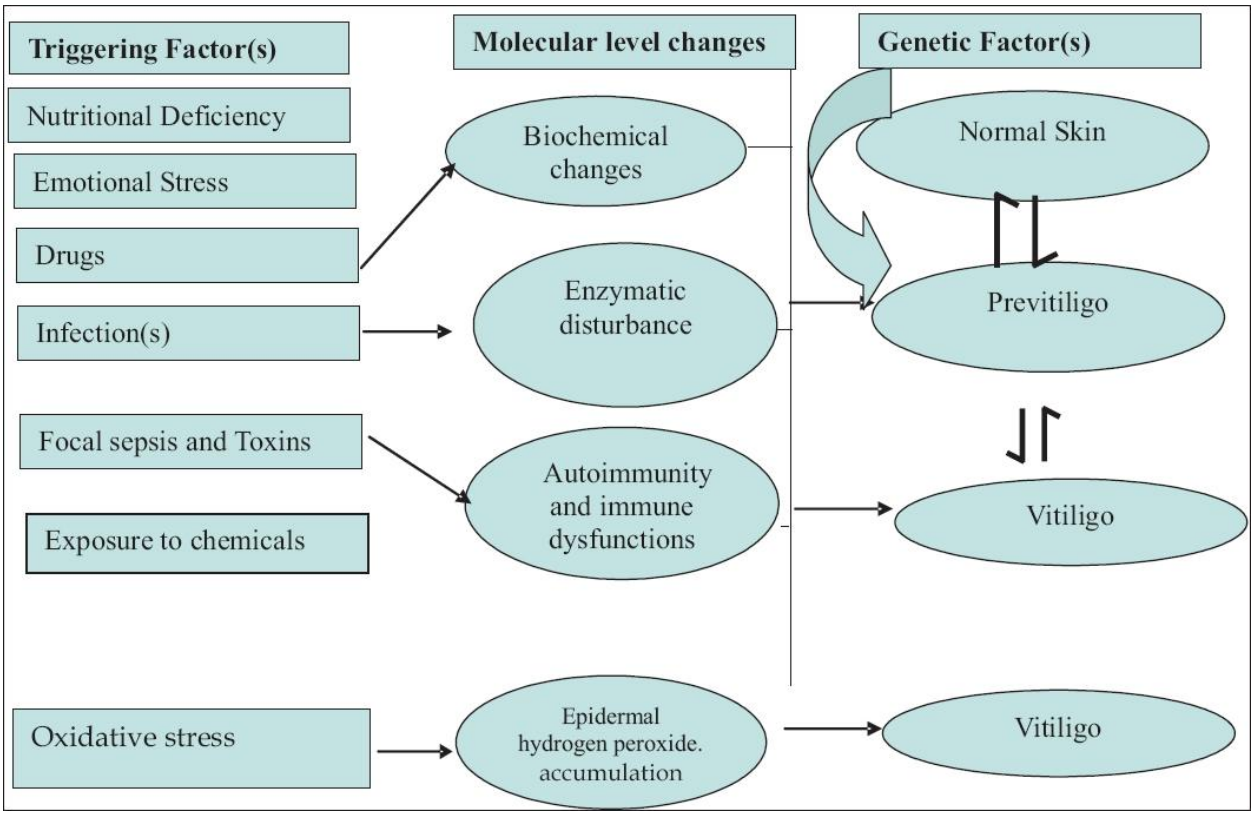

Fig 2: Vitiligo triggering / precipitating factor(s); and their possible role in its pathogenesis [9].

4. Pathogenesis

Vitiligo is a multifactorial disorder characterized by the loss of functional melanocytes.Multiple mechanisms have been proposed for melanocyte destruction invitiligo. These include genetic, autoimmune responses, oxidative stress, generation of inflammatory mediators and melanocyte detachment mechanisms. Both innate and adaptive arms of the immune system appear to be involved. 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. 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 [6].

NSV and SV were believed to have distinct underlying pathogenetic mechanisms due to their different clinical presentations, with the neuronal hypothesis or somatic mosaicism favored for the segmental form [10]. However, more recent evidence points towards an overlapping inflammatory pathogenesis for both SV and NSV. Both seem to involve a multistep process, which involves initial release of proinflammatory cytokines and neuropeptides elicited by external or internal injury, with subsequent vascular dilatation and immune response. Some authors have suggested that the nervous system contributes to vitiligo pathogenesis, referred to as the "neural hypothesis." This hypothesis relied on the unilateral distribution pattern of SV. However, the distribution pattern of SV is not entirely similar to any other skin disease, and it is rarely, if ever, dermatomal [11, 12]. Furthermore, there is not enough evidence to support such a hypothesis. Moreover, melanocyte-specific T-cell infiltrations identical to NSV were found in SV further suggesting that it is also mediated by autoimmunity [13].

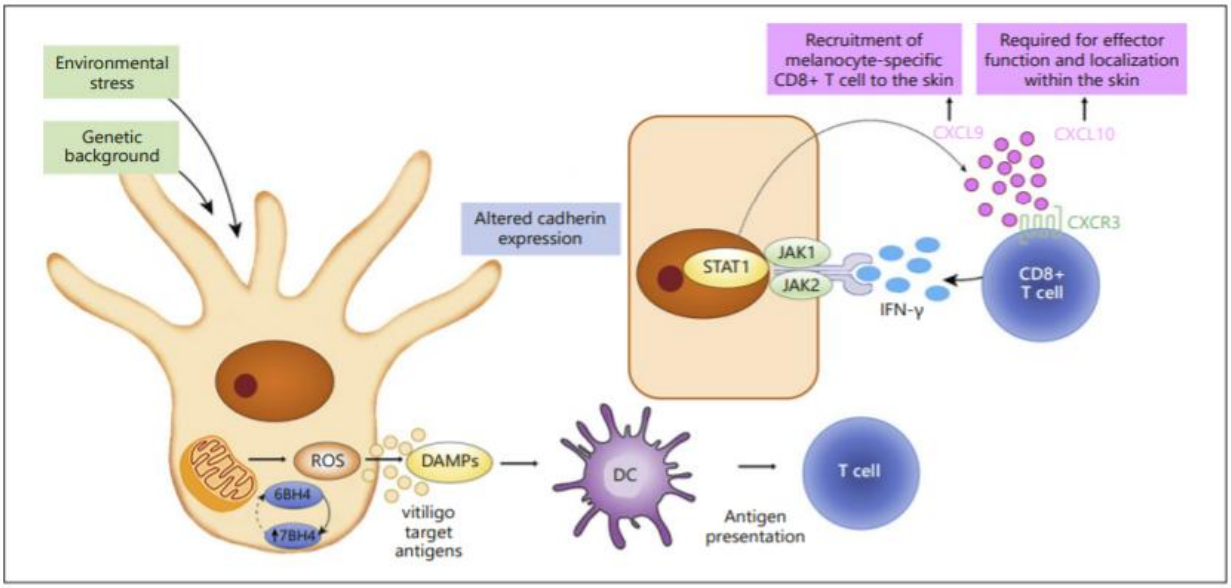

Fig3: Pathogenesisof Vitiligo

In vitiligo, melanocytes from patients with vitiligo have decreased adhesiveness and are more susceptible to oxidative stress. Additional environmental stress, in the presence of a susceptible genetic background, causes widespread alterations of the antioxidant system. Mitochondria seem to be the key inducers of ROS, and patients with vitiligo have an altered mitochondrial functionality. Oxidative stress impairs the function of membrane lipids and cellular proteins. Biopterin synthesis and recycling are also altered, leading to further oxidative stress and cell damage. ROS overproduction activates the unfolded protein response and causes melanocytes to secrete exosomes which contain melanocyte-specific antigens, miRNAs, heat shock proteins, and damage-associated molecular patterns. These exosomes deliver vitiligo target antigens to nearby dendritic cells and induce their maturation into efficient antigen-presenting cells. This is followed by cytokine- and chemokine-driven activation of T helper 17 cells and dysfunction of T regulatory cells. The CD8+ T cells from vitiligo lesions produce several cytokines such as IFN-γ. Binding of IFN-γ to its receptor activates the JAK-STAT pathway and leads to CXCL9 and

CXCL10 secretion in the skin. Through the cognate receptor CXCR3, CXCL9 promotes the bulk recruitment of melanocyte-specific CD8+ T cells to the skin whereas CXCL10 promotes their localization within the epidermis and their effector function, which increases inflammation through a positive feedback loop. 6BH4, 6-tetrahydrobiopterin; 7BH4, 7-tetrahydrobiopterin; CXCL9, CXC chemokine ligand 9; CXCL10, CXC chemokine ligand 10; CXCR3, chemokine receptor type 3; DAMP, damage-associated molecular pattern; DC, dendritic cell; IFN-γ, interferon-γ; JAK, Janus kinase; ROS, reactive oxygen species; STAT1, signal transducer and activator of transcription 1.

4.1 Genetics of Vitiligo

Strong evidence from multiple studies indicates the importance of genetic factors in the development of vitiligo, although it is clear that these influences are complex. Epidemiological studies have shown that vitiligo tends to aggregate in families however, the genetic risk is not absolute. Around 20% of vitiligo patients have at least 1 first-degree relative with vitiligo, and the relative risk of vitiligo for first-degree relatives is increased by 7- to 10-fold . Monozygotic twins have a 23% concordance rate, which highlights the importance of additional stochastic or environmental factors in the development of vitiligo [14]. Large-scale genome-wide association studies performed in European-derived whites and in Chinese have revealed nearly 50 different genetic loci that confer a vitiligo risk . Several corresponding relevant genes have now been identified. They are involved in immune regulation, melanogenesis and apoptosis; they are associated with other pigmentary, autoimmune and autoinflammatory disorders [6]. Several loci are components of the innate and adaptive immune system and are shared with other autoimmune disorders, such as thyroid disease, type 1 diabetes and rheumatoid arthritis . Tyrosinase, which is encoded by the TYR gene, is an enzyme that catalyzes the rate-limiting steps of melanin biosynthesis [15]. Tyrosinase is a major autoantigen in generalized vitiligo . A genome-wide association study has discovered a susceptibility variant for NSV in TYR in European white people that is rarely seen in melanoma patients . It seems that there is a mutually exclusive relationship between susceptibility to vitiligo and susceptibility to melanoma, suggesting a genetic dysregulation of immunosurveillance against the melanocytic system . The NALP1 gene on chromosome 17p13, encoding the NACHT leucine-rich repeat protein 1, is a regulator of the innate immune system. It has been linked to vitiligo-associated multiple autoimmune disease, a group of diseases including various combinations of vitiligo, autoimmune thyroid disease, and other autoimmune and autoinflammatory syndromes [16]. On another hand, the production of large amounts of protein during melanin synthesis increases the risk of misfolding of those proteins, which activates a stress pathway within the cell called the unfolded protein response. XBP1P1 (the gene encoding X-box binding protein 1) has been associated with vitiligo . It plays a pivotal role in mitigating the unfolded protein response, as well as driving stress-induced inflammation in vivo [17]. Although many of the specific mechanisms arising from these genetic factors are still being explored, it is now evident that vitiligo is an autoimmune disease implicating a complex relationship between programming and function of the immune system, aspects of the melanocyte autoimmune target and dysregulation of the immune response [18].

4.2 Oxidative Stress

Research into the pathogenesis of vitiligo suggests that oxidative stress may be the initial event in the destruction of melanocytes . Indeed, melanocytes from patients with vitiligo were found to be more susceptible to oxidative stress than those from unaffected individuals and are more difficult to culture ex vivo than those from healthy controls [19].

Reactive oxygen species (ROS) are released from melanocytes in response to stress. In turn, this causes widespread alteration of the antioxidant system: An imbalance of elevated oxidative stress markers (superoxide dismutase, malondialdehyde, ROS) and a significant depletion of antioxidative mechanisms (catalase, glutathione peroxidase, glutathione reductase, thioredoxin reductase and thioredoxin, superoxide dismutases, and the repair enzymes methionine sulfoxide reductases A and B) in the skin and in the blood . It has been suggested that this imbalance between pro-oxidants and antioxidant in vitiligo is responsible of the increased sensitivity of melanocytes to external pro-oxidant stimuli and, over time, to induce a presenescent status. The generation and buildup of ROS can in turn cause DNA damage, protein oxidation and fragmentation, and lipid peroxidation, thus impairing their cellular function [20, 21].

Both endogenous and exogenous stimuli can potentially generate ROS in vitiligo . The production of melanin itself is toxic to melanocytes. Melanogenesis is an energy-consuming process performed by melanocytes, which generates a pro-oxidant state in the skin . Tyrosine-related protein 1 is an important protein for melanin synthesis. Oxidative stress causes tyrosine-related protein 1 to interact with the calnexin complex, which in turn leads to reduced tyrosine-related protein 1 stability with subsequent production of toxic melanin intermediates . Dihydropteridin reductase is the last enzyme in the recycling process of an essential cofactor 6-tetrahydrobiopterin . Oxidative stress leads to modifications of the active site dihydropteridin reductase which in turn leads to altered biopterin synthesis and recycling [22]. Defective recycling of 6-tetrahydrobiopterin increases production of hydrogen peroxide and decreases catalase levels, which further contributes to cell death.

Mitochondria seem to be the key inducer of ROS, and patients with vitiligo have an altered mitochondrial functionality [23]. An alteration in the mitochondrial transmembrane potential and in the electron transport chain complex causes a marked increase in the expression of mitochondrial malate dehydrogenase activity and a modification of the membrane lipid components. Oxidative stress impairs the function of membrane lipids and cellular proteins . Redox variations of membrane lipids disturb lipid rafts, which disrupt the function of membrane receptors, and electron transfer and ATP production in mitochondria . Furthermore, oxidative stress promotes the expression of the transient receptor potential cation channel subfamily M member 2 and thus facilitates mitochondria dependent apoptosis of melanocytes by increasing calcium influx [24].

Exogenous stimuli can also generate oxidative byproducts . Monobenzone is the most widely used depigmenting agent; it has been shown to induce the release of melanosomal related antigen-containing exosomes following overproduction of ROS from melanocytes .

Decreased melanocyte adhesiveness due to oxidative stress has been detected at the borders of vitiligo lesions possibly explaining the Koebner phenomenon . Melanocyte-keratinocyte interaction does not require specific adhesive structures such as desmosomes, but simple adhesion molecules such as integrins and cadherins. In nonlesional skin of patients with vitiligo, the expression of e-cadherins is decreased and that of tenascin, an antiadhesion molecule, increased . In vitiligo skin, chronic friction can activate epithelial cells, which in turn convert the mechanical forces into biochemical signals , producing intracellular stress and subsequent altered cadherin expression [25].

4.3 Innate Immunity

Innate immunity in vitiligo bridges the gap between oxidative stress and adaptive immunity in vitiligo. It is likely that the activation of innate immune cells occurs early in vitiligo, by sensing exogenously or endogenously induced stress signals released from melanocytes and possibly keratinocyte . As mentioned above, there is an association between vitiligo susceptibility and genetic changes in NALP1, a regulator of the innate immune system . Genomic expression analysis on the skin of patients with vitiligo has highlighted an abnormally heightened innate immunity in the local microenvironment of melanocytes in vitiligo skin, particularly natural killer cells . Indeed, natural killer cells have been found to infiltrate clinically normal skin of patients with vitiligo, suggesting that natural killer cells are early responders to melanocyte stress [26].

Melanocytes seem to communicate stress to the innate immune system through the excretion of exosomes. Human melanocytes were found to secrete exosomes in response to chemically induced stress . These exosomes contain melanocyte-specific antigens, miRNAs, heat shock proteins and other proteins that act as damage-associated molecular patterns . These exosomes deliver vitiligo target antigens to nearby dendritic cells and induce their maturation into efficient antigen-presenting cells . Among these damage-associated molecular patterns, inducible heat shock protein 70 is unique as it acts as a chaperone to peptides specific to the originating host cells that protects cells from undergoing apoptosis [27]. Inducible heat shock protein 70 has been shown to play a central role in vitiligo pathogenesis in a mouse model by inducing dendritic cells to present melanocyte-specific antigens to T cells in lymphoid tissues . This has been proposed to be the key link between innate and adaptive immunity leading to the T cellmediated autoimmune destruction of melanocytes . A modified version of inducible heat shock protein 70, Hsp70iQ435A, was found to repigment vitiligo lesions in Sinclair swine recently, opening the door to a potential new treatment for vitiligo patients [28].

4.4 Adaptive Immunity

Both humoral and cell-mediated immune abnormalities are implicated in the pathogenesis of vitiligo. Antibodies to surface and cytoplasmic melanocyte antigens have been identified in the past in the sera of vitiligo patients . These antibodies can induce the destruction of melanocytes grown in culture by complement-mediated lysis and antibody-dependent cellular cytotoxicity .

Cytotoxic CD8+ T cells that target melanocytes specifically are responsible for the destruction of melanocytes. CD8+ T-cell infiltration of the epidermis and dermis has been demonstrated histologically . Higher numbers of cytotoxic CD8+ T cells are found in the blood of patients with vitiligo compared with healthy controls, and these numbers correlate with vitiligo activity [6]. High numbers of CD8+ T cells are found in perilesional skin, and these cells exhibit antimelanocyte cytotoxic reactivity [29]. Infiltrating T cells isolated from biopsies of the perilesional margins show an enrichment of cells that recognize melanocyte antigens. When these cells were isolated and reintroduced in normally pigmented autologous skin, they induced melanocyte apoptosis . By contrast, CD8+ T cell-depleted perilesional T cells were unable to induce cytotoxicity and apoptosis of melanocytes, whereas CD8-purified populations were even more potent . CD8+ T cells also express the skin-homing marker cutaneous lymphocyte antigen [30]. The destruction of melanocytes was found to be associated with the prominent presence of cutaneous lymphocyte antigen-positive T cells at the perilesional site, the majority of which expressed perforin and granzyme-B. So far, some antigenic proteins derived from normal or stressed melanocytes involved in the melanin synthesis have been identified in vitiligo and include gp100, Melan-A/MART-1, tyrosinase, and tyrosinaserelated proteins 1 and 2 .

The CD8+ T cells from vitiligo lesions produce several cytokines such as interferon-γ (IFN-γ) and tumor necrosis factor, among other cytokines . IFN-γ is central to disease pathogenesis and helps to promote autoreactive CD8+ T-cell recruitment into the skin . The IFN-γ-induced CXC chemokine ligand 9 (CXCL9), CXCL10 and CXCL11 were the most highly expressed genes in a transcriptional profile of lesional skin of vitiligo patients, whereas other chemokine pathways were not [31]. These IFN-γ-induced CXC chemokines were also reported to be increased in the serum of patients . Analysis of chemokine expression in mouse skin showed that CXCL9 and CXCL10 expression strongly correlates with disease activity, whereas CXCL10 alone correlates with severity, supporting them as potential biomarkers for following disease progression. Likewise, serum CXCL10 in patients with vitiligo also correlates with disease activity and severity and may be a novel biomarker in monitoring disease activity [32]. Neutralization of CXCL10 in mice with established, widespread depigmentation leads to repigmentation, suggesting a critical role for CXCL10 in both the progression and maintenance of vitiligo . Indeed, CXCL9 promotes the bulk recruitment of melanocyte-specific CD8+ T cells to the skin whereas CXCL10 is required for localization within the epidermis where melanocytes reside and effector function . Interestingly, both CXCL9 and CXCL10 share a single receptor, CXCR3. Melanocytespecific autoreactive T cells in vitiligo patients express CXCR3 in both the blood and in lesional skin . Targeting CXCR3 in a mouse model using depleting antibodies reduces autoreactive T-cell numbers and reverses the disease [33]. Furthermore, keratinocytes were shown to be the major chemokine producers throughout the course of disease in both

mouse model and human patients . Functional studies using a conditional signal transducer and activator of transcription (STAT) 1 knockout mouse revealed that keratinocyte-derived chemokines and IFN-γ signaling drives vitiligo and proper autoreactive T-cell homing to the epidermis. In contrast, epidermal immune cells such as endogenous T cells, Langerhans cells, and γδ T cells are not required [109]. IFN-γ in turn inhibits melanogenesis and directly induces melanocyte apoptosis [110]. Further functional studies in a mouse model found that IFN-γ, the IFN-γ receptor, STAT1, CXCL10 and CXCR3 are critical for the development of hypopigmentation in vitiligo [6].

Many cytokines that bind type I and type II cytokine receptors use the Janus kinase (JAK) and STAT pathway to achieve their effect [112]. Extracellular binding of cytokines activates their receptors, inducing apposition of JAKs and self-activation by autophosphorylation. Activated JAKs bind STATs, which undergo JAK-mediated phosphorylation leading to STAT dimerization, translocation to the nucleus, DNA binding and regulation of gene expression. In vitiligo, IFN-γ-bound receptor complex recruits JAK1 and JAK2 kinases, leading to phosphorylation and nuclear translocation of STAT, which in turn transcriptionally activates downstream IFN-γ-inducible genes. Lesional skin from patients with vitiligo showed much more intense and diffuse JAK1 expression compared with healthy tissue. Moreover, high JAK1 expression was associated with short disease duration and a lower percentage of surviving melanocytes . These results thereby support investigation of therapies that disrupt the pathway targeting IFN-γ, the IFN-γ receptor, the downstream signaling proteins JAK1, JAK2 and STAT1, and the chemokine CXCL10 and its receptor CXCR3 [34–35].

Regulatory T cells (Tregs) are crucial to the development of self-tolerance. Tregs have been found to be less abundant in vitiligo skin and their functional activity compromised . The paucity of Tregs in vitiligo skin is likely crucial for perpetual antimelanocyte reactivity in this progressive and chronic disease. Indeed, Tregs show lower expression of transforming growth factor β1 in active vitiligo patients . The number of Tregs expressing FoxP3, the transcription factor that downregulates T-cell activation, is reduced significantly in lesional skin . Furthermore, the expression of homing receptor CCL22 was found to be remarkably reduced in vitiligoskin , and conversely, expression of CCL22 can promote Treg skin homing to suppress depigmentation [36].

Functional CD8 tissue-resident memory T cells were found in both stable and active vitiligo, suggesting that those that remain in stable disease could account for the disease reactivation [37]. Figure 1 summarizes the main mechanisms in vitiligo pathogenesis.

Table: 1.A summary of the major theories implicated in the pathogenesis of vitiligo and its

Recent updates

Theory	Genetic theory	Autoimmune hypothesis	Oxidative stress hypothesis	Autocytotoxic hypothesis	Neurohumoral hypothesis
What is known?	Several candidate genes, MHC, ACE, CAT, CTLA-4, COMT, ESR, MBL2, PTPN22, HLA, NALP1, XBP1, FOXP1 and IL-2RA, have been associated with generalized vitiligo	Melanocyte-specific $CD8^+$ T-cells and follicular T helper (Tfh) cells bring about cytotoxic and autoimmune responses against the melanocytes	An alteration of the redox status of skin and blood stream of patients with vitiligo is well known	Environmental exposures and melanin synthesis pathways lead to autocytotoxic damage to melanocytes	Psychological stressors and nervous pathways have an impact on and bring about the release of neuropeptides, which eventually generate melanotoxic by-products
What is new?	*SV: Various new pathogenic genes have been identified separately for SV and NSV.	*The role of IFN γ, IL-17, Th-17 cells, IL-33 and Treg cells is being singly recognized in vitiligo.	*Recent studies have found that the epidermal H_2O_2 level is not increased but rather decreased in patients with NSV	*ROS and UVB bring about the secretion of HMGB1, a non-histone DNA-binding protein, from the keratinocytes which leads to increased production of caspases and subsequent apoptosis of melanocytes	A significant increase in the expression of CRH and CRHR-1 in the lesional and non-lesional skin of patients with vitiligo has been reported as a form of systemic compensation to restore normal pigmentation in vitiligo lesions which, however, fails because of defective melanogenesis pathway in vitiligo lesions
	*The role of microRNAs (miRNAs) and Toll-like receptors (TLRs) has been put forward	*Newer anti-melanocyte antibodies have been found in high titres in patients with NSV	*A decreased activity of Nrf2 ARE and FOX03a protein leading to impaired antioxidant mechanism has been seen in patients with vitiligo		

5. CLASSIFICATION OF VITILIGO

According to the review conducted by the Vitiligo Global Issues Consensus Conference between 2011-2012, vitiligo can be classified in the following clinical forms (Table):2

Type of vitiligo	Subtypes
NSV	Focal[1] Mucosal Acrofacial Generalized Universal Rare variants of vitiligo (leukoderma punctata, hypochromic vitiligo, follicular vitiligo)
SV	Focal[1] Unisegmental Bi- or multisegmental
Mixed (NSV + SV)	Concomitant occurrence of SV and NSV According to severity of SV
Unclassified	Focal at onset, multifocal asymmetrical nonsegmental, mucosal (one site),

[1] Can evolve into segmental (SV) or nonsegmental vitiligo (NSV).

Table:2Classification of vitiligo (adapted from Ezzedine et al.)

5.1 **Non-segmental vitiligo (NSV):** a group that comprises acrofacial, mucosal, generalized or common, universal, and mixed forms besides rare forms.

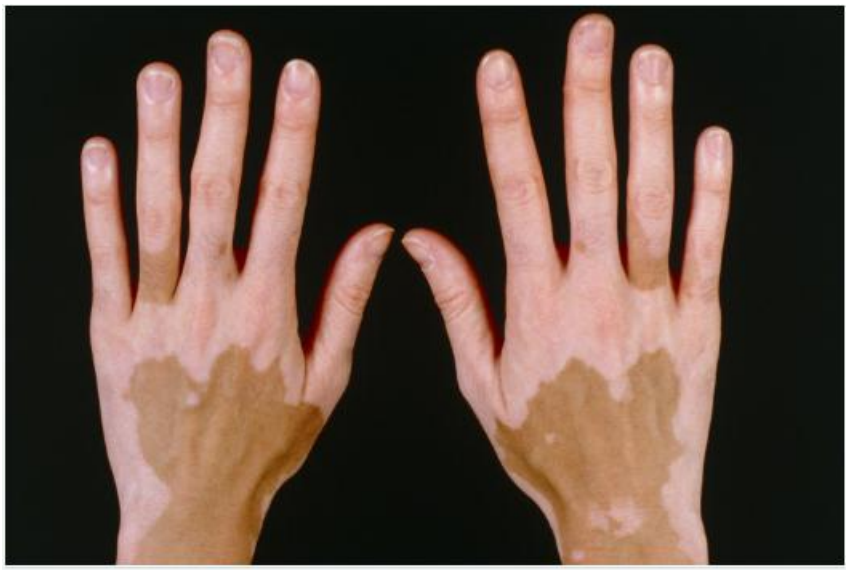

Fig:4 non-segmental vitiligo (also called bilateral or generalised vitiligo)

5.1.1 Acrofacial: it can affect, face, head, hands and feet, and preferably involve the perioral region and the extremities of digits.

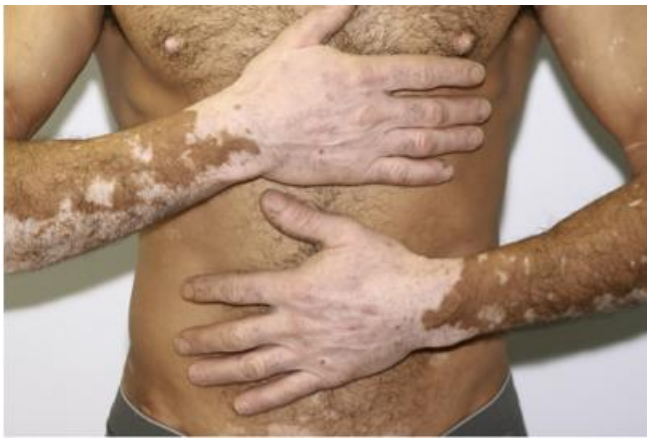

Fig:5 Acrofacial vitiligo, depigmented macules limited periorificial areas, distal extremities and/or the face.

5.1.2 Mucosal: affects the oral and genital mucosae. Furthermore, areas of mucosa may also be affected in patients with acrofacial, common, or universal forms; when it involves only one mucosal site it is classified as indeterminate; l

5.1.3 Generalized or common: Macules / patches are often symmetrical; it can affect any part of the tegument, mainly hands, fingers, face and trauma-exposed areas.

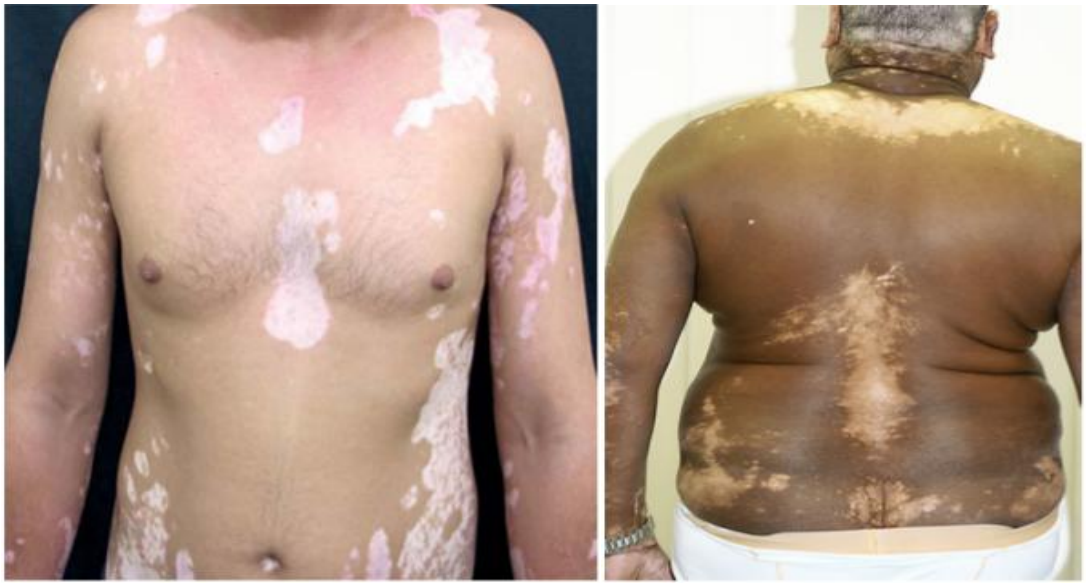

Fig:6 Common Vitiligo. Bilateral and often symmetrical lesions characterize common vitiligo

5.1.4 Universal: is the form that affects the largest extent of tegument (80-90% of body surface), and it is the most common form in adulthood. The generalized or common form usually precedes it.

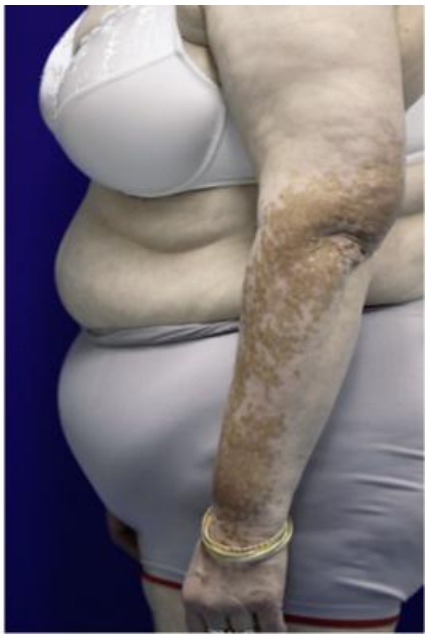

Fig:7Common Vitiligo. Bilateral and often symmetrical lesions characterize common vitiligo

5.1.5Mixed: it is the concomitant involvement of segmental and non-segmental vitiligo. Most often, the segmental form precedes NSV. f. Rare forms: vitiligo punctata, minor and follicular. These types were also considered unclassifiable.

5.2 **Segmental Vitiligo:**

It can affect one, two or multiple segments . The unisegmental form is the most common one and consists of one or more white macules on one side of the body, usually respecting the body midline, and there is also involvement of body hair (leukotrichia) besides rapid onset of the condition. Less commonly, it can affect two or more segments and even have bilateral segmental distribution, starting simultaneously or not.

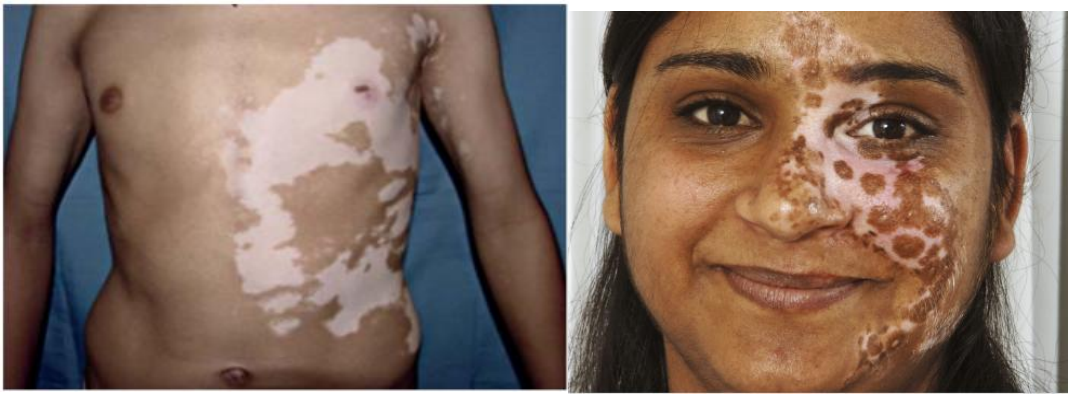

Fig :8 Segmental Vitiligo. Unilateral lesions that respect, almost completely, the body midline, characterize segmental vitiligo. There are rare cases of bilateral segmental vitiligo

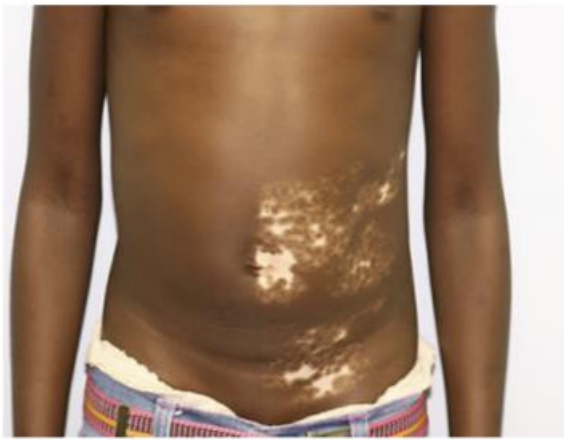

Fig:9 Monosegmental vitiligo of the left abdomen, depigmented patches are usually confined to a single dermatome, with partial or complete involvement.

5.3 **Unclassifiable forms / undetermined vitiligo**

a) Focal: Isolated white macule without segmental distribution. This form can evolve to segmental or NSV forms.

b) Mucosal: when only one mucosa is affected.

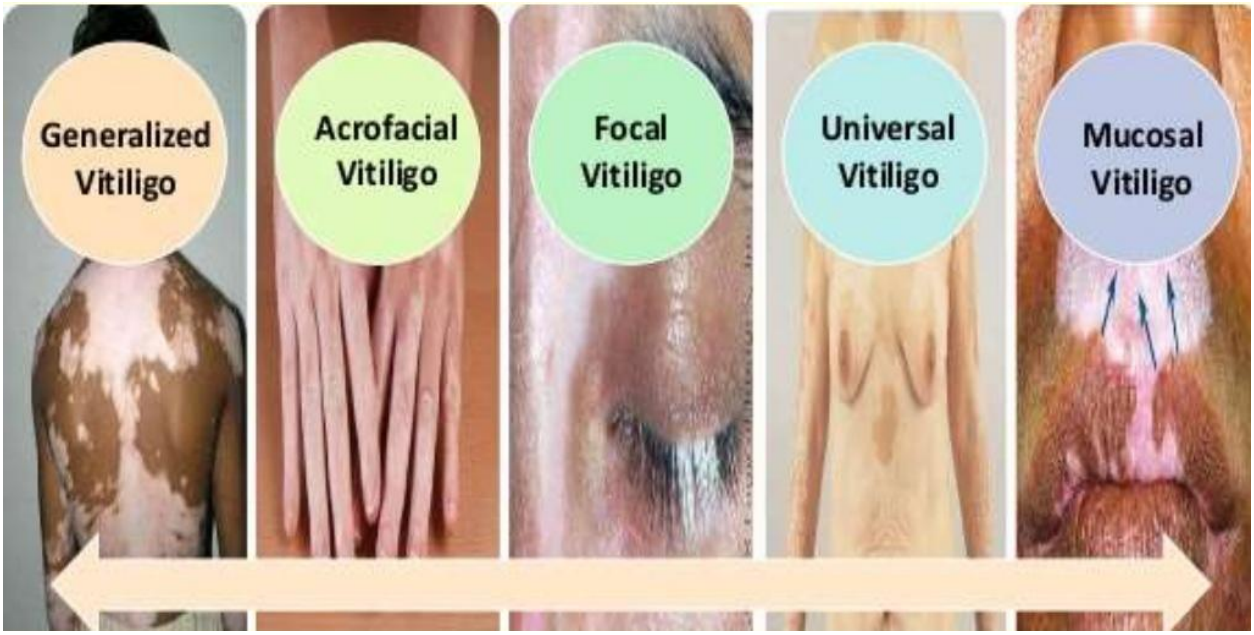

Fig: 10 Types of Vitiligo

6. Symptoms

Vitiligo signs include:

- Patchy loss of skin color, which usually first appears on the hands, face, and areas around body openings and the genitals
- Premature whitening or graying of the hair on your scalp, eyelashes, eyebrows or beard
- Loss of color in the tissues that line the inside of your mouth and nose (mucous membranes)Vitiligo can start at any age, but usually appears before age 30.

Depending on the type of vitiligo you have, it may affect:

- **Nearly all skin surfaces.** With this type, called universal vitiligo, the discoloration affects nearly all skin surfaces.
- **Many parts of your body.** With this most common type, called generalized vitiligo, the discolored patches often progress similarly on corresponding body parts (symmetrically).
- **Only one side or part of your body.** This type, called segmental vitiligo, tends to occur at a younger age, progress for a year or two, and then stop.
- **One or only a few areas of your body.** This type is called localized (focal) vitiligo.

- **The face and hands.** With this type, called acrofacial vitiligo, the affected skin is on the face and hands, and around body openings, such as the eyes, nose and ears.

It's difficult to predict how your disease will progress. Sometimes the patches stop forming without treatment. In most cases, pigment loss spreads and eventually involves most of your skin. Occasionally, the skin gets its color back. [39]

7. Diagnosis

Our dermatologists often diagnose vitiligo based solely on a physical examination. If doctors need more information about how the condition affects your skin cells, they may suggest a skin biopsy or blood test.

7.1 Medical History

Information about your past and current health may help your dermatologist confirm a diagnosis. He or she may ask you when white or lighter patches of skin first appeared and whether they affect several parts of the body or remain in one location. Your doctor may also ask if you have been diagnosed with an autoimmune disorder, such as hypothyroidism or type 1 diabetes, and if any of your family members have a history of vitiligo or an autoimmune condition.

7.2 Physical Examination

Your dermatologist performs a thorough physical examination to determine if vitiligo is affecting your skin and, if so, to identify the type. He or she visually examines your skin from head to toe, noting the places in which depigmentation appears and whether patches appear on one or both sides of the body, symmetrically or in random patterns, and whether they affect only skin exposed to sunlight or areas that are less exposed, as well.

If your skin is very fair, it may be hard to distinguish the depigmented patches caused by vitiligo. In these instances, a dermatologist may use a handheld tool called a Wood’s lamp to shine ultraviolet (UV) light on your skin. A patch of skin that is truly depigmented has a different appearance under the UV light than unaffected skin.

7.3 Skin Biopsy

Your dermatologist may need more information about your skin cells to confirm a diagnosis of vitiligo. A skin biopsy can definitively tell the difference between missing melanocytes, which indicates vitiligo, and melanocytes that are malfunctioning for another reason. Vitiligo is diagnosed only if these pigment-producing cells are missing.

Very rarely, a form of skin cancer called hypopigmented cutaneous T-cell lymphoma may cause white patches due to malfunctioning melanocytes. A skin biopsy can rule out this possibility.

7.4 Blood Test

Rarely, your dermatologist may recommend a blood test to get more information about a possible autoimmune response related to vitiligo. The blood test is done in the office and a doctor or staff member calls you with the result in five to seven days.

8. DIFFERENTIAL DIAGNOSIS

- **Nevus depigmentosus:** It is a circumscribed, segmental depigmented or hypopigmented area present at birth.
- **Pityriasis alba:** It commonly considered as a spectrum of atopic dermatitis and usually affect the children. It presents as white hypopigmented, scaly macules and patches on the face and other photo exposed areas.
- **Idiopathic guttate hypomelanosis:** It is characterized by small, asymptomatic pearly white macules on photo exposed areas. Most of these lesions appear in older age groups.
- **Tinea (pityriasis) Versicolor:** It is a superficial fungal infection that causes loss of pigment. It appears as pale scaly macules present on the back and chest. They give yellow fluorescence under Wood's lamp [
- **Halo nevus**: It is a type of melanocytic nevus surrounded by an oval halo of depigmentation
- **Progressive macular hypomelanosis:** It is clinically present as asymptomatic hypopigmented patches on the trunk of young adults
- **Drug-induced leukoderma:** Potent topical or intralesional corticosteroids can induce hypopigmentation at the site of application. Depigmentation is also noticed in patients treated with the tyrosine kinase and epidermal growth factor receptor inhibitor.
- **Hypopigmented mycosis fungoides:** It is a variant of early-stage MF commonly seen in children and dark-skinned people. It appears as widespread hypopigmented patches with atrophy and scaling and atrophy. [40]

9. TREATMENT OF VITILIGO

Etiology of the Vitiligo is still unknown. But it involves some theories like Auto immunity, cytotoxicity, triggering, neural, free radicals and genetic. It can be treated by oral or topical formulations of the drug alone in mild cases but in severe case of Vitiligo Light therapy is also given with the consumption of medication to increase the pigmentation of the skin. The treatment of leukoderma or Vitiligo requires not only a deposition of pigment in the areas of depigmentation, but it also requires a redistribution of pigment from hyper pigmented borders, so that the result will be an even distribution of the normal amount of cutaneous colouring. It also depends on the presence of the type of the cell. Possibility of formation of melanocyte in inter-follicular epidermis is decreased by the presence of keratinocyte stem cells in the similar location (Rafael, 2009).

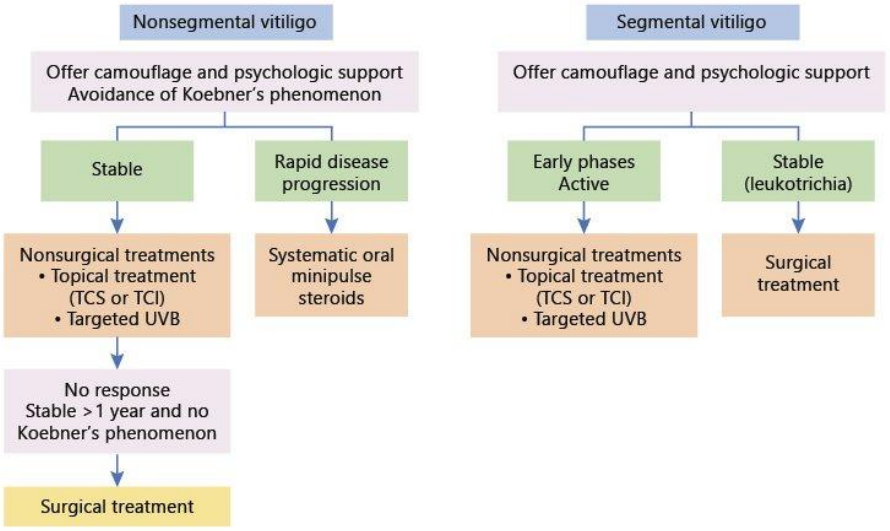

Fig:11 Therapeutic algorithm of vitiligo. TCS, topical corticosteroid; TCI, topical calcineurin inhibitor; UVB, ultraviolet B.

9.1 Treatment of vitiligo with herbal medicines

From the list of Chinese herbs acting for the treatment of vitiligo decoction of xiaobailing changyee powder and threeyellow powders are most effective. These medicines include xanthumstramanum, sophoraflavescens, atractylodes japonica, arisaemaamurense. Some other herbs include carthamustinctorius, eclipta prostrate, pleuroptereesmultiflorees, salvia miltiorrhiza, sesamumindicum, spatholobussuberectus, rehmaniaglutinosa. Applying these medicines onto skin improves skin coloration and treats the vitiligo. Indian herbs involve cassia accidentalis, eclipta prostrate, curcuma longa, picrorrhizakurroa, psoraleacorylifolia, tribulusterrestris. In this mainly photosensitizers and blood purifiers are used. Photosensitizing agents involve psoraleacorylifolia, semicarpusanacardium and ficushispida. They are administered locally as well as systemically with the sun exposure. Blood purifiers include curcuma longa, ecliptaAlba, tinosporacardifolia, hemiclascusindicus, acasia catechu and acaranthusaspara. Exact mechanism of the herbs is unclear but it involves some mechanisms like phototoxic reactions, melanocyte proliferation, promoting anti-inflammatory activity and trigger reduction (Jimi *et al.*, 2011).

S.No	Biological Name of The Plant	Family	Common Name	Active Chemical Constituent
1	*Albizzia lebbek*	Black ebony	Fabaceae	Saponins, stigmastadienone
2	*Aloe barbadensis*	Aloes	Aloeaceae	Antraquinone glycosides
3	*Alstonia scholaris*	Indian devil tree	Apocyanaceae	Hallucinogenic indole alkaloids
4	*Althaea officinalis*	Marshmallow	Malvaceae	Altheacoumarin glycosides
5	*Ammi majus*	Ammi	Umbelliferae	Furanocoumarins
6	*Ammi visnaga*	Khella	Umbelliferae	Furanocoumarins
7	*Angelica sinensis*	Dong quai	Umbelliferae	Ferulic acid
8	*Apium graveolens*	Celery	Umbelliferae	Furanocoumarins
9	*Arisaema amurense*	Tian nan xing	Araceae	Diacylglycerlgalactoside
10	*Aristolochia bracteata*	Bracteated birthwort	Aristolochiaceae	Anthraquinones
11	*Astragalus membranaceus*	Astragalus	Fabaceae	Saponins, flavonoids
12	*Atractylodes japonica*	Japanese	Compositae	Patchoulene

Table: 3 List of name of plant and there active chemical constituents used for treatment of vitiligo

9.2 Traditional Treatment

Red clays found by the river side or on hill slopes can also be used for the treatment of vitiligo. It can be given by mixing with ginger juice. Copper in the clay brings skin pigmentation back and ginger facilitates increased blood flow to the spot which helps into the repigmentation of the spots. Radish seeds powdered with the vinegar and paste is formed. This paste can be applied totreat the vitiligo. Mixture of turmeric and mustard oil which is prepared by heating two of them is also helpful in the treatment of white patches (Priyanka *et al*., 2010).

9.3 Yoga therapy

Kapalbhati is helpful in the treatment of vitiligo. Because ofinhalation and exhalation kapalbhati provides aeration to blood and purifies blood circulation. This is beneficial in different skin diseases like vitiligo, psoriasis and other allergies (Priyanka et al., 2010).

Fig:12 Yoga therapy

9.4 **Homeopathic treatment**

Homeopathy is an alternative medicine originated in germany in 18th century and it is adapted by many countries. Ars.ach, Bacillinum, Graphites, Mercasol, Nat mur, nuxvom, sil, sulph, thuja etc. medicines can be used under homeopathic treatment (Priyanka et al., 2010).

9.5 Ayurvedic treatment

In Ayurveda vitiligo is known as Switra and it is mainly caused due to the Pitta Dosha as aggravated Pitta leads to accumulation of toxins (ama) in deep layers of the skin which leads to the condition of Vitiligo. Basic treatment of this disease includes Calming imbalanced body energies, cleansing blood and administering the herbs which restore the skin colour. Poor digestion cause build-up of toxins into the body thus it is a root cause for the disease. Therefore, restoring digestion is the essential part of the body (Jiva Ayurveda). Generally Ayurvedic treatment of Vitiligo involves four steps. First step is Purification therapies (Shodhana Karma), which includes use of herbal decoction of Psoralea Corylifolia and Eurphorbianerifolia. Second step includes Oil massage, in which oil is selected on the basis of disease state (roga) and Patient Examination (rogiPariksa). Third step is exposure of lesions to the sun rays depending on the tolerance of the patient (Sooryapadasanthapam). And fourth and last step is delivery of decoction (kwatha) made of Ficushispida (malayu), Pterocarpusmarsupium (asana),Calllicarpamacrophylla (priyangu), Peusedanumgraveolens (satapuspa), Coleus vettiveroides (ambhasa), and alkaline extract of Buteamonosperma (palasaksara), along with an alcoholic preparation of jaggery (the preparation is called phanitha in Ayurveda)to the patient. The diet should be salt-free and should contain buttermilk during the treatment of decoction (Saravu et al., 2010). Different ayurvedic formulations of herbs which are available are given in the table:

Type of Ayurvedic Formulation	Probable herbs used
Lepa (Topical preparation)	Ankollakadi, Avalgujadi, Bakucyadi, Balyadi,Bhallatakadi, Bhringarajadi, Gandhakadi,Grhadhumadi, Gunjadi,Gunjaphaladi,Katukalabvadi,Manasiladi,Maricadi, PancaNimbava, Pathyadi, Patrakadi,Putikadi,Talakadi,Triphaladi, and Vayasyadi
Kashaya (Mixtures)	Bakucibeeja yoga, Bakuciprayoga, Bhadrodumbarikadi yoga, Dhatryadikwata, Kakodumbarikakasayaand Khadiradikashaya
Churna (Compound Powder)	Bakucyadyachurna,Kakodumbarikadi yoga, Khadirasaradichurna andPancanimbachurna
Ghrita (Paste)	Dantyadighrita, Mahamarkaraghrita, Mahaneelaghrita, Mahatiktakaghrita, Mahavajrakaghrita, Neelakaghrita, Neelighrita, Neelinyadighrita, Somarajighritaand Tiktakaghrita
Avaleha (Oral Semisolid preparations)	BhallatakavalehaandVidangadileha
Thaila (Oil preparations)	Aragwadhayadyathaila, Citrakadyathaila, Jyotismatithaila, KustaKalanalathaila, Kustaraksasathaila, Laghumaricadyathaila, MahaVajrakathaila, Manasiladyathaila, Maricadyathailaand Vishathaila
Asava Arista (Fermented preparations)	Kanakabindvarista and Madhwasava
Vati/Gutika (tablets)	SwayambhuvaGuggulu, ThriphaladigutikaandBrhatSwayambhuva Guggulu
Rasousadha(Formulations containing processed minerals and metallic salts)	Candraprabhavati, Galitakustari rasa, Khageswara rasa, Kustebhakesari rasa, Medanisara rasa, Pittalarasayana, Talakeshwara rasaand Vijayeswara rasa

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9.6 Topical allopathic treatment

Fig: 13 Topical allopathic treatment

Generally, the first-line pharmacologic treatment for vitiligo is topical corticosteroids (CSs), which can be applied to most skin lesions. The efficacy of CSs is attributed to the drugs'

modulation of immune response. Vitiliginous lesions on the neck and face respond better to CSs than lesions in other areas; however, the use of CSs on the face is limited because of the thinness of the skin and subsequent increased absorption. Potent and highly potent products (TABLE 4) are recommended over less potent agents.Potent CSs such as betamethasone valerate should be tried first, and only if the patient does not respond should high-potency CSs such as clobetasol propionate be used. Of note, high-potency CSs should be used for only 1 to 2 months, after which time they should be slowly tapered to a lesser strength. In one study, 10% of patients prescribed clobetasol propionate 0.05% achieved near-complete repigmentation, as opposed to 25% of those treated with betamethasone valerate 0.1%. High-potency CSs should be applied in a thin layer once daily to the depigmented area only, as this will help reduce the risk of side effects such skin atrophy, striae, steroid folliculitis, hypertrichosis, and acne. Systemic absorption is also a concern, especially in patients with thin skin, those with large areas of depigmentation, those with head or neck vitiligo, and children. Potential systemic side effects include insomnia, agitation, weight gain, and adrenal insufficiency.

Table: 4. Potent and Highly Potent Corticosteroids

Potency	Generic Name	Brand Name
Highly potent (also termed *superpotent* or *ultrahigh potency*)	Augmented betamethasone dipropionate 0.05%	Diprolene, Diprosone
	Clobetasol propionate 0.05%	Clobex, Olux,[a] Temovate,[a] Temovate E[a]
	Diflorasone diacetate 0.05%	Apexicon[a]
	Halobetasol propionate 0.05%	Ultravate[a]
Potent (also termed *high potency* or *intermediate potency*)	Amcinonide 0.1%	Cyclocort
	Betamethasone valerate 0.1%	Beta-Val,[a] Luxiq
	Desoximetasone 0.25%	Topicort[a]
	Diflorasone diacetate 0.05%	Apexicon E[a]
	Fluocinolone acetonide 0.2%	Synalar
	Halcinonide 0.1%	Halog
	Triamcinolone acetonide 0.5%	Kenalog, Aristocort A

[a] *A generic version is available.*
Source: References 13, 14.

Calcineurin inhibitors (CIs)—pimecrolimus 1% and tacrolimus 0.03% or 0.01%—are another effective topical choice. CIs provide immunomodulatory effects without the side effects of CSs, but with similar efficacy. As with CSs, lesions of the head and neck respond best to CIs. The application of hydrocolloid dressings in conjunction with the use of CIs has been shown to enhance repigmentation of resistant arm and leg lesions. Common side effects associated with CIs include erythema, pruritus, burning, and irritation. CIs are typically dosed twice daily and are approved for short-term use (2-4 weeks) or intermittent long-term use. CIs are considered alternatives to topical steroids because of similar efficacy and a better tolerated side-effect profile. Also, CIs may be used in patients with lesions on the face or neck, areas where steroid therapy is less desirable.

A third topical immunomodulatory agent is calcipotriene, a vitamin D analogue that enhances the development of melanocytes in vitiligo. Although calcipotriene has been shown to be inferior to topical CSs for monotherapy, it may be an effective adjunctive treatment. When calcipotriene is

combined with CSs, the rate of repigmentation increases, the delay to repigmentation onset shortens, and there is greater stability of repigmentation compared with either agent alone. Erythema, dryness, stinging, and burning have been reported as the most common side effects of calcipotriene use.

9.7 Surgical therapies

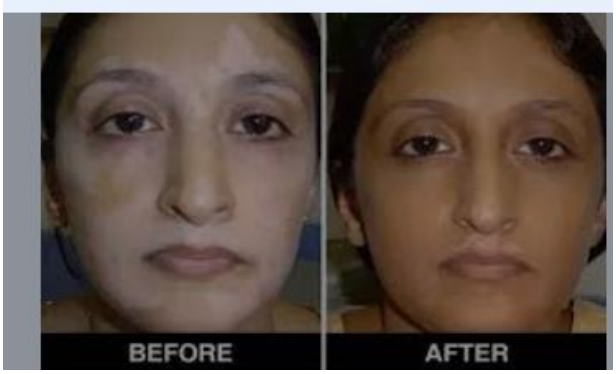

Fig: 14 Image before & after surgical therapy

In surgical therapies white patches are treated with the help of different surgeries. It involves different mechanisms of surgery. In Autologous Skin Grafts technique grafts are implanted into perforations prepared at the recipient sites. Patients with segmental vitiligo are best candidate for this type of grafting. In blister grafting blisters are used. These blisters can be induced by different ways such as vacuum or liquid nitrogen. At the dermoepidermal junction the mechanical split occurs and the graft is secured on the recipient site. Primarily a cobblestone appearance and limited treatment area per session are the limitations of the above two mechanisms. To overcome these limitations epidermal cell transplantation can be done. This technique involves application of a melanocyte-rich suspension to the affected area and then it is allowed to graft. Only one time treatment is necessary is the main advantage to this technique. Micro pigmentation (Tattooing) technique involves permanent dermal micro pigmentation. It is done by using a non-allergic iron oxide pigment. These pigments provide colour to the skin (Priyanka et al., 2010; Navneet et al., 2012).

9.8 Other alternative treatments

If no treatment works for the treatment than alternative cover-ups can be used. Leukodermic skin easily gets damaged to the sunburn and the effect lasts for very long time. So to avoid the excess exposure to the sunlight and prevent the sunburn sunscreens can be used. To hide the untreated white patches onto the skin cosmetics cover-ups are very useful (Priyanka et al., 2010; Navneet et al., 2012).

9.9 Depigmentation

It is a drastic form of treatment for vitiligo. It involves fading the rest of the skin of the body so the whole body appears in white colour. For that permanent melanocytotoxic agents like monobenzyl ester of hydroquinone cream and 4-methoxyphenol can be used. (Navneet et al., 2012)

9.10 Photo chemotherapy

Application of photochemical reaction is an advantageous for the treatment of vitiligo. Photochemotherapy is Traditional therapy for Vitiligo. This therapy is based on ancient Atharva Veda observations. Psoralen is having very good photochemical response to ultraviolet B as well as ultraviolet A. Because of this reason the treatment includes topical/oral psoralen treatment, followed by exposure to ultraviolet light or Sunlight. This combined treatment is known as PUVA therapy (Psoralen Ultraviolet A therapy). It is based on the observation in Atharva Veda more than 3000 years ago. In this treatment oral psoralen is administered followed by UVA rays exposure. This is FDA approved treatment of Vitiligo and psoriasis. Psoralens are compounds found in many plants. These compounds make the skin temporarily sensitive to UVA. For oral treatment of PUVA, methoxsalen capsules are taken before two hours of the appointment.

There is significant but saturable first-pass elimination in liver, which may cause variations in plasma levels after a standard dose. Methoxsalen has a serum half-life of one hour, but the skin remains photosensitive for 8-12 hours. During this therapy, the patient has to stand in a cabinet containing 24 or more UVA fluorescent bulbs having length of 6 feet. To protect the eyes from the exposure of radiation, the patient should always wear goggles. PUVA promotes melanogenesis in normal skin. Increased pigmentation results from augmented transfer of melanosomes from melanocytes to keratinocytes. PUVA has some side effects like Burning, Itching, Nausea, Tanning and painful erythema. In topical treatment gel or cream of psoralen is applied and then exposure of uv light is given. Dark skin types have better repigmentation than paler skin types. Topical PUVA is an attempt to limit the area that becomes photosensitized (Priyanka *et al.,* 2010; Navneet *et al.,* 2012; Laurence and John, 1941; Bhawna *etal.,* 2012).

9.10.1 Mechanism of drug psoralen

Psoralen is having good photosensitizing characteristics. So it is used in many types of treatments like herbal, alternative, photochemotherapy, topical etc. The exact mechanism of action of psoralen (Methoxsalen) with the epidermal melanocytes and keratinocytes to enhance pigmentation into the body is not known. One biochemical reaction of Psoralen (methoxsalen) is known with DNA. Methoxsalenafter conjugation forms covalent bonds with DNA. The conjugation leads to formation of monofunctional and bifunctional adducts. This occurs due to photo activation of the Methoxsalen. In above reaction Methoxsalen acts as a photosensitizer and cause pigmentation of the skin. Through the blood orally administered methoxsalen reaches to

the skin and UVA penetrates well into the skin. Themelanocytes present in the hair follicle are stimulated to move up the follicle and to repopulate the epidermis and thus become helpful in the treatment of vitiligo (Laurence and John, 1941).

9.11 Other Drugs used for the treatment

Trioxsalen is given orally. By increasing skin pigmentation, it increases the tolerance of the skin to UV light. This drug sometimes causes cutaneous reaction. Methoxsalen can be given orally as well as topically. In oral dosage form 20mg/day drug is given 2-4 hours before UV exposure. It causes gastric discomfort. In topical dosage form 0.1% to 1% lotion is applied and sun light or UV light exposure is given. It may cause Acute, Vesicular, Cutaneous photosensitivity reaction. Both the formulation of this drug may cause severe sunburn (Satoskar et al., 1969).

Fig: 15 Name of drug generally used on vitiligo treatment:

Albaquin

Triox 2

Flozin 25 Triox Lotion

Lucoderm-5

Review of Literature

S. NO.	Author Name	TITLE	KEYWORD	PUBLICATION YEAR
1	michelle rodrigues	New discoveries in the pathogenesis and class infaction of vitiligo	chemical leucoderma confect depigmentation halo nevi leucoderma	2020
2	Shigeki ikeya	introduction to vitiligo and its treatment	Vitiligo, Melanocytes, Skin disorder, Repigmentation Treatment.	2020
3	SR Mercuri	Protective and pathogenic	resident memory T cell	2019

		roles of resident memory T cells in human skin disorders	skin disorders	
4	Cristina fortes	Melanoma and Vitiligo: In Good Company	melanoma; autoimmunity; prognostic markers	2019
5	anuradha bishnoi	Clinical and Molecular Aspects of Vitiligo Treatments	vitiligo; stabilizing treatments; repigmenting treatments	2018
6	Cheng-che E. Lan	Mechanisms of repigmentation induced by photobiomodulation therapy in vitiligo	mechanism, melanocyte precursors, photobiomodulation therapy, repigmentation, vitiligo	2018
7	Katia Boniface	Vitiligo: Focus on Clinical Aspects, Immunopathogenesis, and Therapy	. Pathophysiology . Immunopathology . Therapy	2017
8	Amit .G. Pandya	New discoveries in the pathogenesis and classification of vitiligo	chemical leukoderma; confetti depigmentation; halo nevi; leukoderma; segmental vitiligo; vitiligo; vitiligo pathogenesis	2017
9	Haroon Khan	A holistic review on the autoimmune disease vitiligo with emphasis on the causal factors	Autoimmune disease Melanin loss Thyroid gland Tyrosine	2017
10	Luciana paula Samorano	Tuberous sclerosis complex: review based on new diagnostic criteria	Diagnosis; Hamartoma; Sirolimus; Tuberous Sclerosis	2017
11	Iltefat Hamzavi	New discoveries in the pathogenesis and	chemical leukoderma; confetti depigmentation;	2017

		classification of vitiligo	halo nevi; leukoderma; segmental vitiligo; vitiligo; vitiligo pathogenesis	
12	Mehdi Rashighi	Vitiligo Pathogenesis and Emerging Treatments	_ Vitiligo _ Cellular stress _ Autoimmunity _ Chemokines _ Targeted therapy _ Melanogenesis	2016
13	Stanca A. Birelea	Trends in Regenerative Medicine: Repigmentation in Vitiligo	vitiligo; repigmentation; melanocyte stem cell; melanoblast; regeneration	2016

10. CONCLUSION:

Normally, the color of hair and skin is determined by melanin. Vitiligo occurs when cells that produce melanin die or stop functioning. Vitiligo affects people of all skin types, but it may be more noticeable in people with darker skin. The condition is not life-threatening or contagious. It can be stressful or make you feel bad about yourself.An international consensus classified segmental vitiligo separately from all other forms of vitiligo, and the term vitiligo was defined to designate all forms of nonsegmental vitiligo. Treatment for vitiligo may restore color to the affected skin. But it doesn't prevent continued loss of skin color or a recurrence. The application of psoralens and different derivatives of psoralens with potentially fewer acute side effects has been one of the most recent advancements in the treatment of leucoderma. Psoralen containing plants have been used for centuries in popular medicine to treat leucoderma, a skin disease characterized by lack of pigmentation. Further advancement in treatments using different derivatives of psoralen molecules should strive to decrease the possibility of long term side effects such as cutaneous malignancies.

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