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Research Article

Immunological Mechanisms and Advanced Diagnostic Techniques in Vitiligo: A Comprehensive Review

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Abstract

Many people believe that vitiligo, an acquired depigmenting sickness marked by the selective loss of melanocytes, is an immune-mediated illness. Immunological markers may improve diagnostic accuracy and offer insight into disease activity and development, despite the fact that clinical examination is still the mainstay of diagnosis. Vitiligo is a long-term, acquired depigmenting condition that causes distinct white macules and patches due to a focal loss of functioning melanocytes. Even though vitiligo's clinical characteristics are widely known, its complicated pathophysiology entails a complex interaction between immunological dysregulation, oxidative stress, and genetic predisposition. There is mounting evidence that vitiligo is primarily an autoimmune condition brought on by innate and adaptive immune responses that target melanocytes. Important immunological processes include increased reactive oxygen species that lead to cellular stress, aberrant activation of innate immunity cells including natural killer cells and dendritic cells, and the resulting generation of cytotoxic T lymphocytes that are specific to melanocytes. Cytokine networks, including interferon-γ and the CXCL9/10 chemokine axis, which promote T cell recruitment and melanocyte death, further contribute to the breakdown of immunological tolerance. Chronicity of the disease is also influenced by altered antigen presentation and dysfunctional regulatory T cells. Diagnostic methods for vitiligo such as imaging techniques like ultraviolet light photography, reflectance confocal microscopy, computer-assisted imaging analysis, optical coherence tomography, visible light and digital photography, colorimetry, spectrometry and immunological diagnosis. We conclude that the comprehension and clinical assessment of vitiligo have been greatly improved by recent developments in diagnostic tools.

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Introduction

Vitiligo is defined as an illness marked by the skin's loss of melanin pigment as a result of melanocyte death or dysfunction [1]. The progressive loss of epidermal melanocytes in vitiligo, an acquired autoimmune depigmenting disease, causes noticeable white patches on the skin. About 2% of people worldwide are affected, and the frequency is increasing annually [2]. Current study focuses on genetic changes, environmental factors, oxidative stress, immunological responses, and neural theories because the true pathophysiology of vitiligo is unknown [3]. Melanocyte-specific damage is primarily caused by cytotoxic T lymphocyte overactivation, regulatory T lymphocyte malfunction, and aberrant cytokine expression [4]. Corticosteroids successfully arrest disease development and promote “repigmentation” in many individuals, On the other hand, minocycline controls disease activity and shields melanocytes from oxidative damage in vitro [5]. The causes of vitiligo are still not clearly understood; it is the result of the interplay of several pathological factors that contribute to the disease's occurrence. Therefore, several theories have been proposed to explain the appearance of this disease, one of which is the immunological theory, oxidative stress theory and genetic [6]. The researcher [7] indicated the important immune role in the occurrence of vitiligo, as it was found that there is an increase in the concentration of the chemokine CXCL10 and its role in the infiltration of CD8 T-cells into the affected areas and their effectiveness in killing melanocytes. The CXCL10 released from the vicinity of vitiligo-affected cells attracts T cells to those areas and subsequently attacks the melanocytes, confirming the role of the cellular immune response in the development of vitiligo [8]. Other studies have shown a relationship between certain autoimmune diseases and the onset of vitiligo, where it was found that autoimmune thyroid disease is common among vitiligo patients at a rate of 0% to 52% [9]. [10] noted that individuals with autoimmune thyroid disease possess autoantibodies against thyroid antigens, and it was observed that these antibodies can attack antigens present on melanocytes, leading to their destruction. This demonstrates how the humoral immune response contributes to the development of vitiligo. According to the oxidative stress theory, the elevated level of reactive oxygen species (ROS) is one of the causes of the disease by increasing the accumulation of the oxidative agent hydrogen peroxide (H2O2) in the melanocyte cells of the skin of patients suffering from vitiligo. The accumulation of these factors contributes to the pathophysiology of the disease [11]. [12] state that oxidative factors can either originate from external environmental sources due to exposure to certain chemicals like phenols or from internal sources related to metabolic processes occurring in the body. The study by [13] highlighted the role of autoimmunity in the onset of vitiligo, indicating the involvement of antibodies in the disease's occurrence as well as the contribution of other immune cells in attacking melanocytes. The research presented by [14] revealed the role of immunity in the disease and noting that vitiligo skin lesions are characterized by the infiltration of immune cells such as T cells and macrophages. Lymphocytes appear in the lesioned areas at an early stage of the disease, indicating their role in the progression of the disease and the appearance of spots in the lesioned areas of vitiligo, the humoral immune response and the efficacy of antibodies against antigens of pigmentary cells in the serum of vitiligo patients were also revealed [15]. Increased production of main pro-inflammatory cytokines, including TNF-α, IL-2, IL-6, and IL-8, has been shown in laboratory investigations, highlighting and its role in attacking and destroying melanocytes, and what further supports these studies is the increase in IL-2 levels in the blood serum and in the skin ulcers of the affected areas, which in turn raises the levels of T cells [16].This review aims to present an overview of the current understanding of vitiligo's clinical characteristics and immunological mechanisms, highlight diagnostic techniques, point out research gaps, and offer suggestions for better early

detection, disease monitoring, and tailored treatments.

Definition and History of Vitiligo

Vitiligo has been known for a long time, but its origins have not been determined. It was found in Pharaonic artifacts (1500 BC) in papyrus manuscripts describing two skin diseases that were prevalent at that time, the first description was of leprosy, and the other was a description of the loss of color from human skin, which is related to vitiligo, originating from the Greek word "Vitius," which meaning "defect," in the sense of harm or imperfection, the term "vitiligo" was first used in the second century AD by the Roman physician Celsus. It is still used in medical dictionaries today [17].

The skin

The skin is a complex organ that covers and protects the body from external influences and pathogens. It also protects itself from ultraviolet rays by producing melanin, relying on pigment-producing cells that absorb light and heat [18]. The epidermis, dermis, and hypodermis are the three primary layers that make up the skin. The four main layers that comprise the epidermis are the granular layer (Stratum granulosum), the spinous layer (Stratum spinosum), the cornified layer (Stratum corneum), and the basal or germinative layer (Stratum basale or germinativum). The epidermis contains various types of cells, including keratinocytes, Merkel cells, Langerhans cells, and melanocytes, Merkel cells, Langerhans cells, melanocytes and Leukocytes [19].

Skin melanocytes

Melanocytes are found on the basal layer of the epidermis and have dendritic processes with long and short protrusions that extend or spread between the keratinocytes of the upper layer. These dendrites enable melanocytes to connect with keratinocytes to transfer melanin pigment, and cellular connections between cells stimulate melanocyte proliferation and differentiation because the keratinocytes produce growth factors [20]. The skin contains other pigments such as carotenoids and hemoglobin derivatives (Hemoglobin derivatives), and these pigments, along with melanin, contribute to the skin's color, However, the main pigment in the skin is melanin [21]. Ultraviolet rays play a fundamental role in affecting skin color, causing variations in skin pigmentation [22].

Etiologies of Vitiligo

Vitiligo is considered a chronic and non-contagious skin disorder that appears as white patches of varying sizes and shapes. It can affect both genders and any age group, and its cause is unknown. However, recent scientific evidence suggests that it is an autoimmune disease [23]. Furthermore, a meta-analysis of nine studies indicated a lower incidence of keratinocyte carcinoma in vitiligo patients [24]. Vitiligo and skin cancer risk are inversely correlated. A lower chance of vitiligo and an increased risk of melanoma, basal cell carcinoma, and squamous cell carcinoma are linked to a number of genetic polymorphisms in the Tyr, MC1R-DEF8, and RALY-EIF2S2-ASIP-AHCY-ITCH loci [25]. Vitiligo therapy requires striking a careful balance between a proclivity for autoimmunity and the benefits of robust immunosurveillance, such as effective antitumoral and antiviral protection, to attain the best possible immunological response. Since overtreatment of the immune system is likely to raise the risk of viral infections and cancer, it should be avoided [26]. Melanocytes and keratinocytes can produce reactive oxygen species (ROS) in response to UV radiation, external injury, and inflammation [27]. Stressed melanocytes and keratinocytes respond by producing chemokines. C-X-C motif chemokine ligands (CXCL)9, CXCL10, CXCL12, CXCL15, CXCL16, and Regulated on Activation, Normal T cell-Expressed and -Secreted (RANTES), which are elevated during illness flare-ups, are associated with a T helper 1 response and the recruitment of cytotoxic T cells [28]. Compared to "healthy" melanocytes, vitiligo melanocytes may be less able to express immunological checkpoints such PD-L1, which would decrease their

resistance to immune-mediated death [29]. Attribute the white color characteristic of vitiligo patches to the absence of melanocytes responsible for producing melanin, which gives color to the skin and hair, as a result of the absence of these cells, the skin lacks the primary source of pigment, leading to the skin turning white. Studies have shown that this disease is associated with several factors and causes, including the immune system's role in destroying pigment cells. Studies have shown that this disease is associated with several factors and causes, one of which is the immune role in destroying melanocytes, as the results of the electron microscope examination indicate degeneration in keratinocytes, melanocytes, and Langerhans cells from the basal membrane layer, accompanied by inflammation with the infiltration of mononuclear cells, cytotoxic T-cells, and macrophages from the blood to the dermis [30]. The immunological, neurological, and biochemical theories of vitiligo's etiology have been developed. Then, a few years ago, the convergence theory was put up to combine the various hypotheses of vitiligo development into a single summary of the etiology of vitiligo [31]. These theories include:

Autoimmune theory

The immune system has the basic defense mechanism in protecting the organism's body against pathogens. However, when the immune system's activity exceeds its normal limits, it fails to recognize the body's organs, and immune cells produce various cellular activities and antibodies that participate in attacking the body's tissues and cells, treating them as if they were foreign. This type of unwanted response against self-antigens is called autoimmunity. The diseases and abnormal conditions that result from this response are called autoimmune diseases [32].

Oxidative Stress Theory

The oxidative stress hypothesis explains how vitiligo occurs. This theory is also known as the autoimmune degeneration theory of melanocytes, which refers to the role of oxidizing agents. Free radicals, or oxidizing agents such as superoxide (O2-), hydrogen peroxide (H2O2), and nitric oxide (NO), are generated. These molecules are produced through normal physiological conditions within the body and their production increases in certain pathological conditions [33].

Genetic theory

Studies confirming the role of immune factors in the onset of vitiligo have led many researchers to explain the immune causes and attribute them to hereditary factors responsible for immune response and inflammatory immunity. These factors result in some changes occurring in specialized genes responsible for expressing those immune components. A genetic study, using various genetic techniques, revealed the presence of genetic variations and mutations in many of those genes responsible for producing immune components that attack body cells, including melanocytes in the skin [34].

Neural theory

This theory assumes the existence of an acute disorder in the nerves supplying the pigment cells, as certain neurochemical mediators are released at the nerve endings in the skin, leading to a disruption in the function of the pigment cells, which results in their destruction or inhibition of melanin production. Supporting this is the distribution of some vitiligo cases along the paths of certain nerves, as well as the prevalence of vitiligo among those who have experienced psychological and neurological crises [35].

Viral theory

This theory confirms that the appearance of vitiligo is associated with the body's infection by certain viral diseases such as hepatitis C, herpes simplex I [36]. Meanwhile, other studies have shown that the body's infection with viral diseases may cause an immune system disorder, making it prone to producing antibodies and cytotoxic lymphocytes against melanocyte [37]. Other viruses, including the

Epstein-Barr virus, hepatitis E and C viruses, HIV, herpes viruses, herpes zoster virus, and CMV, point to a critical role for viral hypothesis in the pathophysiology of vitiligo through aberrant immune system modulation. The function of the Epstein-Barr virus, cytomegalovirus, and herpes simplex virus in producing these illnesses has been the subject of numerous investigations [38]. Immune dysregulation is probably involved in both vitiligo and varicella zoster virus (VZV) infection. Melanocytes are destroyed by the immune system in vitiligo, presumably as a result of T lymphocytes attacking melanocyte antigens. By changing the immunological response, VZV infection can make this autoimmune onslaught worse [39].Viral-induced Inflammation: Infection with VZV causes a potent inflammatory reaction that is characterized by the production of chemokines and cytokines. In vitiligo lesions, this inflammation may exacerbate pre-existing damage or encourage melanocyte loss [40, 41].

Classification of Vitiligo

Vitiligo is classified based on the shape and properties of the disease. The researcher [42] divided vitiligo into the following categories based on its forms:

1. Segmental vitiligo (Vitiligo zosteriform): It is described by its initial appearance, quick development, and then stopping after one or two years of spreading. The patches spread along the body or in a linear fashion.

2. Non-segmental vitiligo: This type is the most common and appears on both sides of the body and in areas most exposed to the sun, such as the face, hands, and neck. It includes the following types:

Gender

Although vitiligo affects both sexes equally, some research indicates that women are more likely than boys to have it, particularly in girls [46].

A. Localized vitiligo (Vitiligo areate):

The number of visible spots on the body ranges between 1-2 and is divided into Focal or Partial, Localized

B. Facial and acral vitiligo (Vitiligo acrofacialis): The spots spread on the face, lips, hands, and feet.

C. Generalized vitiligo (Vitiligo vulgaris): It is divided into generalized and universal, and it spreads throughout the entire body.

D. Mucosal vitiligo (Vitiligo mucosal): This type is special as it only spreads in the mucous membranes.

Prevalence of vitiligo

Vitiligo is widespread across the entire world, with a global prevalence rate of 2%. The highest incidences of vitiligo have been recorded in India and Mexico. Some attribute the high incidence of vitiligo in these countries to dietary habits and the types of chemicals the populations are exposed to [43]. In a study conducted in Iraq on the causes and spread of vitiligo, it was found that a high incidence of the herpes simplex labialis virus, which affects the lip area and around the mouth, leaving a scar, is a contributing factor. In some individuals infected with this virus, depigmentation occurs in the affected area, which contributes to the development and appearance of vitiligo on the face [44].

Age

In Iraq, the average age of vitiligo patients begins at 17 years, but 6% of patients experience disease progression before the age of 20. Additionally, 25% of patients have a family history of vitiligo [45].

Vitiligo and autoimmunity

Higher recurrence of vitiligo in the presence of autoimmune disorders such as thyroid dysfunction, pernicious anemia, and diabetes. This is because the presence of these diseases generates autoantibodies that may participate in attacking and destroying melanocytes through immune-mediated killing [47]. Alopecia areata and thyroid illness are the most common auto-immune conditions associated with segmental vitiligo. NSV had greater incidence of auto-immune illnesses than SV, particularly thyroid disease [48].

Vitiligo and humoral immune response

Studies conducted on the sera of vitiligo patients using immunoprecipitation and immunofluorescence techniques have shown an increase in the concentration of antibodies, particularly IgG. Two-thirds of vitiligo patients produce antibodies against melanocytes (Anti-melanocytes) in the circulatory system [49].

Crucially, the pathogenesis of many autoimmune diseases, including vitiligo, is intimately linked to B cells. In order to destroy infections or mark antigens, Initially, active B cells mature into plasma cells, which release IgG and IgM antibodies [50]. Significantly, vitiligo patients' epidermis has more B cells, and patient sera contain a variety of melanocyte-specific antibodies linked to disease activity. Clinical research indicates that certain autoimmune illnesses, like systemic lupus erythematosus, may profit from B cell depletion therapies like the anti-CD20 antibody rituximab [51].

Vitiligo and cellular immune response

Many inflammatory and histological studies of the cankerous areas of the skin in vitiligo patients have demonstrated the infiltration of various types of immune cells, especially cytotoxic T-cells, helper T-cells, and macrophages. This infiltration represents the most prominent immune response in the peripheral areas of the skin before the external morphological appearance of vitiligo becomes clearly visible on the skin. Lymphocytes appear at an early stage of the disease, and these lymphocytes are immature and unspecialized in the epidermis and dermis, indicating their role in disease progression and the appearance of spots in the cankerous areas [52].

Vitiligo and Oxidative Stress

Oxidative stress, which results from an imbalance between oxidants and antioxidants, generates a range of free radicals that can damage DNA, proteins, lipids, and carbohydrates [53].

Vitiligo and autoimmune thyroid diseases

The existence of shared heritable susceptibility genes is suggested by the documented correlation between vitiligo and AITD [54]. There are over 15 susceptibility genes for AITD and 37 for vitiligo [55]. Nine loci that may be associated in both vitiligo and AITD were found by candidate gene association studies and genome-wide linkage analysis [56]. Organ-specific genes including those that code for TYR, Tg, and TSHR are among them [57]. The most likely cause of the co-occurrence of vitiligo and the fork head transcription factor D3 is one of the 27 genes that correspond to the AIS1 locus [58]. A single nucleotide polymorphism of the PTPN22 gene, which codes for a lymphoid-specific phosphatase, is also present in vitiligo and AITD patients [54].

Diagnosis Imaging techniques

Ultraviolet light photography

A common and widely used diagnostic method for assessing vitiligo is ultraviolet (UV) light. Seven of the examined investigations used UV light as a diagnostic method, In six of them, Wood's lamp is the suggested choice [59]. Wood's light, commonly known as a Wood's lamp, is the most widely used UV light diagnostic tool for vitiligo. It is a portable gadget with a magnifying lens to allow for near skin examination and long-wave UV radiation (wavelengths of 320–450 nm, peak 365 nm) [60]. Additionally, a basic hand-held black

light source—more precisely, a crude flashlight—was used in one investigation by [61]. In comparison to a typical Wood's lamp, this investigation shown that the hand-held source was equally effective at highlighting skin lesions or detecting fluorescence [62] evaluated the accuracy of vitiligo lesion identification by dermatologists and patients with and without Wood's light. The researchers found that dermatologists can find good candidates for grafting by looking at amelanotic lesions with distinct boundaries under Wood's lamp, which is a stability sign. Additionally, using Wood's lamp makes it easier to identify re-pigmentation early on, allowing for precise monitoring and assessment of treatment results [63].

Reflectance confocal microscopy

Eleven studies employed reflectance confocal microscopy (RCM) to diagnose vitiligo and track treatment outcomes [64]. When it comes to stable vitiligo, The damaged skin's melanin content and dermal papillary rings both totally vanish. Along with the loss of dermal papillary rings, melanin is also lost in active vitiligo [65].

Computer-assisted imaging analysis

Several methods for computer-assisted image analysis of vitiligo are currently being researched. Twenty papers that used variations of computer-assisted image analysis for vitiligo diagnosis were found through the literature search. Convolutional Neural Networks (CNNs) have been used in eight investigations and have demonstrated encouraging results in vitiligo diagnosis [66]. CNNs consistently outscored all human raters, including general practitioners, dermatology residents, and practicing dermatologists. This demonstrates the effectiveness of machine learning in vitiligo case probability classification or in the absence of a Wood's light, as well as the potential benefits of CNN approaches as a remote vitiligo diagnosis tool in telemedicine circumstances [67]. In one study, skin depigmentation was measured using artificial neural networks (ANN) of the multilayer perceptron (MLP) type based on the pattern of light refraction [68]. The MLP was trained to evaluate each pixel in an image and categorize it as having either healthy or damaged skin based on the light refraction pattern. The original image is then converted into a binary image using the MLP, with cells containing 0 and 1 denoting healthy and vitiligo-affected skin, respectively. The recommended method outperformed both ICA/PCA and FCM in sensitivity and specificity across an 8-test period [68].

Optical coherence tomography

A non-contact technique for three-dimensional imaging of a sample's internal microstructure and topology is optical coherence tomography (OCT). OCT can be used to access internal biological organs using endoscopes, small-diameter catheters, an ocular scanner, or a traditional microscope [69]. Visual evoked potentials (VEPs) and optical coherence tomography (OCT) are trustworthy paraclinical techniques that can detect acute and prior optic nerve damage linked to multiple sclerosis. to supplement Montalban and colleagues' 2024 modifications to the McDonald criterion [70]. OCT can accurately diagnose vitiligo in its initial phases, according to a study by [71]. This was achieved by reconstructing a three-dimensional skin microstructure using OCT for in vivo imaging. This successfully identified any color loss in the early stages of vitiligo, even though white patches of skin only become apparent in the later stages of the condition [71]. [72] reached a similar outcome, demonstrating the effectiveness of OCT in vitiligo early diagnosis.

Novel Three-Dimensional Imaging Platform for Digital Facial Vitiligo Area Assessment

Clinical trials employ subjective scoring techniques, such as the face Vitiligo Area Scoring Index (F-VASI), to gauge the degree of face skin depigmentation in vitiligo patients; however, these evaluations are very variable and have limited sensitivity. Here, we created a unique digital 3D imaging technology to quantify vitiligo lesions and quantitatively evaluate changes in facial vitiligo [73]. For example, the Vitiligo Extent Score (VES) and the Vitiligo Area Scoring Index (VASI) are two commonly used methods to assess the efficacy of treatment in the degree of vitiligo [74]. These techniques are primarily intended to assess the degree of depigmentation throughout the entire human body. The facial VASI (F-VASI) score was created expressly to measure facial depigmentation in order to assess the effectiveness of treatment for facial vitiligo [75].

Colorimetry

A non-invasive tool for measuring skin tone, the colorimeter has also been used to assess pigmentation potential. Colorimetry provides a systematic method for assessing the stability of the disease and enables the objective measurement of vitiligo-related epidermal alterations. Colorimetry offers important insights into the development and response to therapy of vitiligo by accurately measuring factors including brightness value and melanin index. The colorimeter's potential function and effectiveness as a non-invasive diagnostic tool for determining the severity of vitiligo are demonstrated in two articles [76].

Spectrometry

Patients with vitiligo can have their disease activity evaluated using these non-invasive methods. Spectrometers are portable instruments that use optical signals with a high spectrum resolution to study the morphological and physiological characteristics of skin tissue [77].

Immunological diagnosis

Since cytokine imbalance is a major factor in the pathophysiology of vitiligo, the anti-inflammatory cytokine interleukin-10 (IL-10) and the pro-inflammatory cytokine IL-17 were identified using Enzyme Linked Immunosorbent Assay (ELISA) technique kits to investigate their potential as biomarkers of disease activity (78). Additionally, kits for the Enzyme Linked Immunosorbent Assay (ELISA) technique were used to measure the levels of cytokines (IL-17A and TNF-α) and total IgE. The Single Radial Immunodiffusion (SRID) method was used to identify immunoglobulins (IgM, IgG, and IgA) [79].

Conclusion

Despite these advancements, standardizing diagnostic biomarkers and incorporating experimental results into normal clinical practice continue to present difficulties. Large-scale validation studies, the development of tailored immunotherapies based on individual immunological signatures, and the integration of multimodal diagnostic techniques should be the top priorities for future research. Improving long-term results for vitiligo patients and promoting tailored therapy will require a deeper comprehension of immunological pathways in conjunction with sophisticated diagnostic techniques.

Different immunological alterations linked to vitiligo are correlated with the disease's clinical manifestations. Combining clinical assessment with specific immunological biomarkers may improve diagnostic precision and advance knowledge of illness pathophysiology.

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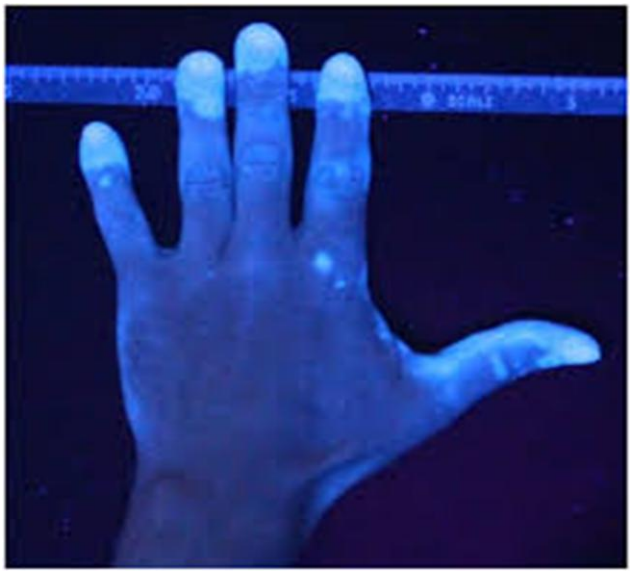

Figure (1): Ultraviolet light photography

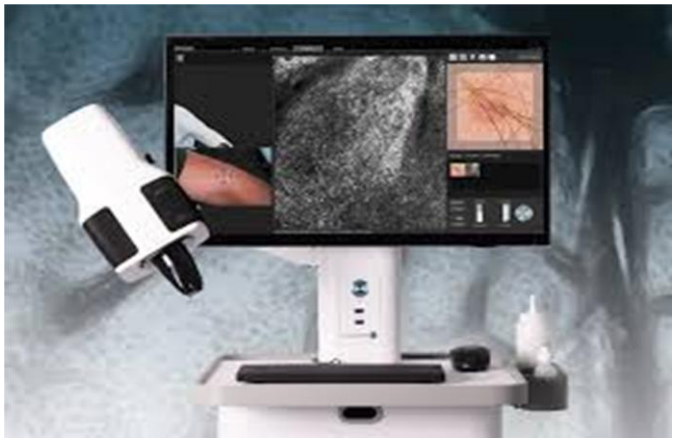

Figure (2): Reflectance confocal microscopy

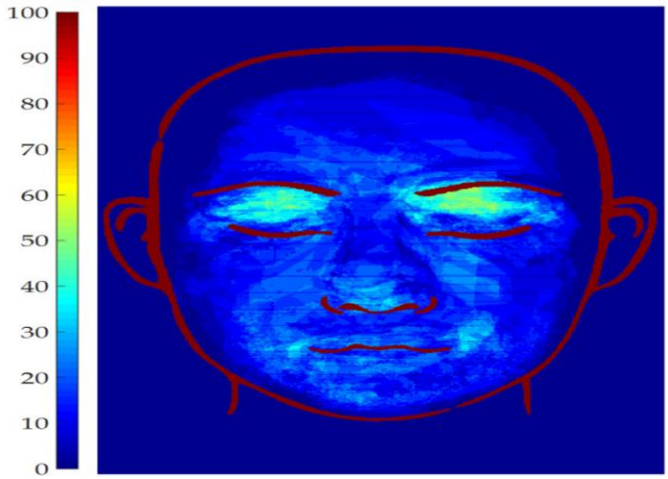

Figure (3): Computer-assisted imaging analysis

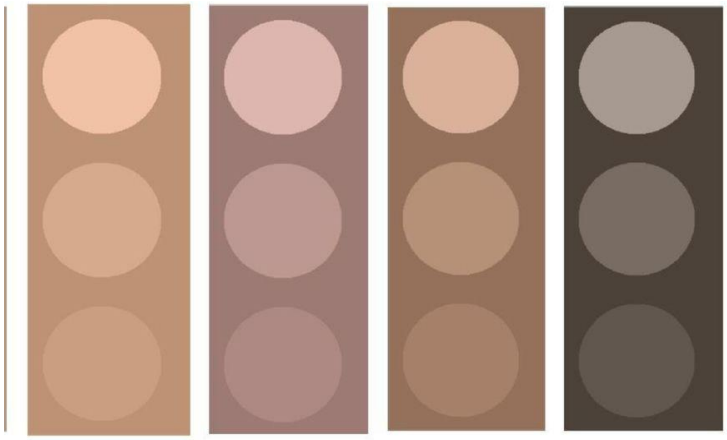

Figure (4): novel Three-Dimensional Imaging Platform for Digital Facial Vitiligo Area Assessment