Review on Assessment and Evaluation of Vitiligo in Primary Care

Abstract:

Vitiligo is an acquired skin disorder characterised by the disappearance of melanocytes, resulting in well-defined white patches that are frequently symmetrically distributed. The lack of melanin pigment makes the lesional skin more sensitive to sunburn. Vitiligo can be cosmetically disfiguring, and it is a stigmatising condition that can lead to serious psychologic problems in daily life. Vitiligo is treated with a variety of topical and systemic medications, phototherapy, laser therapy, and surgical therapy. Corticosteroids, calcineurin inhibitors, and vitamin-D analogues are examples of topical treatment modalities. Phototherapy is a highly effective treatment method. It causes repigmentation in the majority of patients with early and localised disease. Because vitiligo is associated with other autoimmune disorders, a multidisciplinary approach is required. Collaboration and communication between primary care physicians and dermatologists are critical. This review aims to assess role of primary care physicians in assessment and management of vitiligo in primary care settings.

Introduction

The most frequent acquired depigmenting condition is vitiligo. It has a strong societal stigma but is treated as a near-orphan disease in terms of medical care. It affects about 1–2% of the population. This condition is characterized by a restricted range of symptoms including macules or patches that are depigmented and correlate to a significant loss of epidermal function and, in some cases, hair follicle melanocytes [1-3.] Adults and children are both afflicted, and there is no gender preference [4].

Vitiligo is now clearly classified as an autoimmune disease, with hereditary and environmental variables, as well as metabolic, oxidative stress, and cell detachment abnormalities, Vitiligo should not be ignored as a cosmetic or trivial disease, as its psychological repercussions can be severe, and it can have a significant impact on everyday life.[5-7]. When vitiligo appears after puberty, it usually affects the face and distal extremities, and it's more likely to be connected with other autoimmune diseasees.

Vitiligo is classified into segmental or non-segmental with the second one being the more common. Multiple subtypes of non-segmental vitiligo exist, including focal vitiligo, generalized vitiligo, and acrofacial vitiligo, among others, based on the body regions where lesions appear and how they proceed. Upon examination, however, all kinds have a similar clinical appearance. Segmental vitiligo is a type of vitiligo that affects one specific part of the

body. It is usually unilateral and does not reach the midline. This type of vitiligo, which accounts for 5% to 30% of all instances, is often linear or block like in appearance and most commonly affects the face, neck, trunk, limbs, and scalp. Most cases of segmental vitiligo begin in childhood, progress fast in the affected area over the course of 6 months to 2 years, and then stabilize for the rest of the patient's life.[8,9]

While Non-segmental vitiligo includes three sub-classifications which are: **focal Vitiligo**, Where lesions appear in one specific location of the body and do not spread to other parts of the body, nor do they broaden or change over the course of two years. This kind of vitiligo is most similar to other non-extensive diseases such segmental vitiligo or nevus depigmentosus. **Acrofacial vitiligo** includes sparse lesions that occur bilaterally over the face and on the distal extremities, where it might appear as amelanotic macules bilaterally, similar to localised vitiligo. Truncal lesions are rarely found in the early stages of acrofacial vitiligo, but they may emerge as the acrofacial variety progresses to generalised vitiligo.[8]

Vitiligo that has spread throughout the body. Lesions in **generalized vitiligo** appear in many parts of the body and frequently begin as acrofacial or localized lesions before evolving to a widespread appearance in a bilateral, typically symmetrical pattern. The skin, body hair, and even oral/genital mucosae become nearly completely depigmented as widespread vitiligo progresses. The disorder is termed as universal vitiligo when the depigmentation reaches this level.[10,11]

The prevalence of depression in a comparison group was given in eleven researches. Psoriasis patients were the most common comparator, with five trials involving 172 vitiligo patients. Only one study was able to match the control and vitiligo subjects (by sex and education)[12]. People with vitiligo had a lower overall risk of depression than those with psoriasis; the pooled relative risk was 066 (95 percent CI 048–090); there was no heterogeneity Healthy controls were the second most prevalent comparator (n = 4 studies; however, only two of them revealed the prevalence of depression in the comparator groups). Depression was shown to be more common in vitiligo patients than in healthy controls in both investigations. In the study, the healthy controls and individuals with vitiligo were close in terms of age and sex, although not in the study done by Karia et al .[14]

Epidemiology and Causes of Vitiligo:

In 1977, one of the biggest and greatest epidemiological surveys was conducted on the Danish island of Bornholm, where vitiligo was found to affect 0.38 percent of the population [15]. Vitiligo affects persons of all racial backgrounds and skin types equally.
However, there appear to be significant geographical disparities. For example, a study in China's Shaanxi Province found a prevalence of 0.093 percent, whereas rates in India were as high as 8.8 percent This high figure may reflect the inclusion of cases with toxic and chemical depigmentation Furthermore, the variation in prevalence numbers could be

attributed to higher data reporting in locations where social and cultural stigma are prevalent, or where lesions are more visible in those with dark skin.[16-20]

Males and females are evenly impacted, however women seek help more often than men and boys, probably due to the larger negative social impact NSV can affect persons of all ages, however it is more common in young people between the ages of 10 and 30 . Twenty-five 25 percent of vitiligo patients get the disease before the age of ten, nearly half of vitiligo patients get the disease before the age of twenty, and about 70–80 percent of vitiligo patients develop the disease even before age of thirty [21-24].

Vitiligo is a multifactorial condition in which functioning melanocytes are lost The elimination of melanocytes in vitiligo has been attributed to a variety of processes. Genetics, autoimmune reactions, oxidative stress, inflammatory mediator production, and melanocyte detachment processes are among them. The immune system's innate and adaptive parts appear to be engaged. None of these proposed ideas are sufficient in themselves to explain the many vitiligo phenotypes, and the total impact of each of these processes is still up for debate, despite the fact that the autoimmune nature of vitiligo is now widely accepted. The steady loss of melanocytes could be caused by a variety of causes, including immunological attack or cell degeneration and detachment.
Multiple mechanisms may operate together in vitiligo to contribute to the loss of melanocytes, eventually leading to the same clinical result, according to the "convergence theory" or "integrated theory."[25-30]

Multiple studies have found that genetic factors have a significant role in the occurrence of vitiligo, while it is obvious that these influences are complex. Vitiligo seems to concentrate in families, according to epidemiological research, however the hereditary risk is not absolute. Around 20% of vitiligo patients have at least one first-degree family member who also has the disease, and the incidence rate of vitiligo for first-degree relatives is increased by 7 -10-fold .The incidence rate of monozygotic twins is 23%, highlighting the involvement of extra stochastic or environmental variables in the development of vitiligo [31-33].

Several genes that are related to each other have now been discovered. They play a role in immunological modulation, melanogenesis, and apoptosis, and they're linked to a variety of pigmentary, autoimmune, and auto-inflammatory diseases.[34-38] Tyrosinase, that is coded by the TYR gene, is a melanin biosynthetic enzyme that catalyzes the rate-limiting stages .In widespread vitiligo, tyrosinase is a prominent auto-antigen In European white people, a genome-wide association study found a susceptibility variation for NSV in TYR that is infrequently seen in melanoma patients .There appears to be a completely unique link between vitiligo and melanoma susceptibility, implying a genetic dysregulation of immunosurveillance against the melanocytic system.[34-37]

According to studies on the pathophysiology of vitiligo, oxidative stress may be the first step in the loss of melanocytes [Moreover, melanocytes isolated from vitiligo patients are more

vulnerable to oxidative stress from those from healthy controls, and they are more difficult to cultivate ex vivo than melanocytes from healthy controls.[38,42] Melanocytes release reactive oxygen species (ROS) in reaction to stress. As a result, an imbalance of elevated oxidative stress markers (superoxide dismutase, malondialdehyde, ROS) and a notable reduction of antioxidative processes (, glutathione peroxidase, catalase, glutathione reductase, thioredoxin reductase, superoxide dismutases, and methionine sulfoxide) It has been claimed that in vitiligo, the imbalance between pro-oxidants and antioxidants account for the increased sensitivity of melanocytes to external pro-oxidant stimulations and, over time, the induction of a presenescent state[43-47] .ROS production and accumulation can lead to DNA damage, protein oxidation and fragmentation, and lipid peroxidation, all of which impede cellular function [48,49].

In vitiligo, innate immunity crosses the barrier between oxidative stress and adaptive immunity. Early in the course of vitiligo, innate immune cells are likely to be activated by exogenously or endogenously produced stress signals emitted by melanocytes and perhaps keratinocytes there is a link between vitiligo susceptibility and genetic alterations in NALP1 (also known as CARD7, DEFCAP, and NAC), an innate immune system regulator The local microenvironment of melanocytes in vitiligo skin exhibits abnormally elevated innate immunity, notably natural killer cells, according to genomic expression analyses on the skin of patients with vitiligo .Natural killer cells have been discovered infiltrating clinically normal skin of vitiligo patients, implying that natural killer cells are early responders to melanocyte stress.[50-52] Melanocytes excrete exosomes, which appear to signal stress to the innate immune system. Exosomes are secreted by human melanocytes in exposure to chemically induced stress .Exosomes contain antigens specific to melanocytes, miRNAs, heat shock proteins, and some other proteins that operate as damage-related molecular patterns.[53]

Immune disorders of the adaptive immunity, both humoral and cell-mediated, have been linked to the development of vitiligo. Antibodies to surface and cytoplasmic melanocyte antigens have previously been found in vitiligo patients' serum. By complement-mediated lysis and antibody-dependent cellular cytotoxicity, these antibodies can kill melanocytes produced in culture. Melanocyte destruction is caused by cytotoxic CD8+ T lymphocytes that specifically target melanocytes. Histological evidence of CD8+ T-cell infiltration of the epidermis and dermis has been found. Vitiligo patients have a higher number of cytotoxic CD8+ T cells in their blood than healthy controls, and these counts correspond with vitiligo activity. [54-58]

Assessment and Evaluation in Primary Care:

For the diagnosis and assessment of skin disorders, a variety of procedures are available. These techniques, we believe, can be categorized as follows:
1 Subjective, semi-objective, and objective; 2 Microscopic or. Macroscopic; and 3 Morphometric or Colorimetric.

Clinical assessment by a dermatologist, visual comparisons of skin tissue before and after using the treatment (using non-digital or digital images taken under visible or UV light), and a vitiligo disease activity score (VIDA) are all examples of subjective approaches . The Vitiligo Area Scoring Index (VASI) and point counting are two semi-objective methodologies. Software-based image analysis, tristimulus colorimetry, spectrophotometry, and confocal laser microscopy are some of the objective ways (CLM). photography in natural or UV light, photography with computerized image analysis, or spectrophotometry are all examples of macroscopic morphological measurement. CLM is a non-invasive micro -morphological procedure that includes CLM. It is characterized by an accurate determination of the hue and chroma of the substructures of pigmented lesions.[59,60]
The majority of techniques are concerned with morphometry. The exception is the chromameter approach, which evaluates colorimetry. Furthermore, some image analysis software can evaluate both morphometry and colorimetry.

1- Subjective methods

These techniques use clinical examination or the analysis of pictures taken at various intervals throughout treatment to determine the percentage of improvement. However, a consensus on a suitable scoring system is required to allow for subjective and trustworthy visual interpretation of outcomes. This standardized scoring method will allow for reliable and suitable data gathering that can be used for direct comparisons as well as pooling treatment findings from various clinical studies. Furthermore, clinicians' interpretations of treatment results appear to differ widely, and patients should have some say in defining a therapeutic consensus.[61]

Visible light photography: Serial images taken over time can reveal information about the development of the disease or the response to treatment. For medical record-keeping and instructional purposes, traditional visible light photography using standard 35-mm film has long been the preferred way of capturing photos of the skin. In exceptionally fair-skinned people, however, it can be difficult to discern between hypomelanosis and amelanosis under visible light using photography. this method has the advantages of being Quick and easy. [62,63]

Ultraviolet light photography: UV photography is related to the fact that melanin in the epidermis absorbs UV rays more selectively than visible light. By focusing UV light at the patient's skin, Wood's lamp is used to diagnose skin problems. A portion of the emitted fluorescence reaches the skin's surface, but it is absorbed by haemoglobin in capillaries and epidermal melanin. This method improves the assessment of the amount of pigment disorders by enhancing epidermal pigmentation changes that are not detectable in visible light. this method has the advantages of being more clear and can give the physician more information about the activity and extent of the vitiligo.[64,65]

Vitiligo disease activity score: It is a six-point scale used to evaluate the stability of vitiligo over time. It is based on the patient's report about its own disease activity. It aids in determining the efficacy of therapies in terms of stopping and halting the progression of depigmentation as Vitiligo can be active or passive. the active vitiligo includes either the emergence of new lesions or the growth of existing lesions [66,67]

2- Semi-objective methods

Vitiligo area scoring index: The VASI was developed by Hamzavi et al. and is a prototype. based on the PASI score (Psoriasis Area and Severity Index) It is frequently used to evaluate psoriasis. The VASI is a sensitive, standardized method for determining the level and percentage of depigmentation. The VASI divides the patient's body into five sections. and regions that are totally exclusive: the hands, upper extremities (With the exception of the hands), trunk, lower extremities (excluding the feet) as well as the feet. The buttocks are considered with lower extremities. the face and neck are evaluated but not included in the results The VASI is calculated for each body region as the product of the area of vitiligo in hands units (set at 1% every unit) and the extent of vitiligo depigmentation within each patch assessed in hand with values ranging between 0, 10, 25, 50, 75, 90 or 100%. this method is known for being easy and has the ability to measure the extent of depigmentation and repigmentation. [68]

Point-counting method: To calculate the volumes of organs or structures, the point-counting method is employed to estimate the irregularly shaped sectional surface area. With an ordinary ballpoint pen, the lesion borders are marked, and a sheet of paper is immediately placed over the lesion. The copied bounds of the projection areas are improved for each lesion by redrawing the outlines with a pen. A translucent sheet with a point (+) written on it is randomly placed on the lesion projection region to estimate the number of points. The number of junctions that pass through the target area is counted. Each lesion's total area is calculated by multiplying the representative area of a grid point by the total number of points counted for the lesion. On the grid, each + symbol has a surface area of 0.1 cm2. this method is mostly used to estimate the surface area of irregular shapes.[69-71]

3- **Objective methods:**

Colorimetry-based image analysis: The tristimulus colorimeter has been demonstrated to be effective in a number of recent experiments. it is highly helpful in determining the severity of UV-induced erythema and pigmentation, disease severity, and therapy efficacy . It's perhaps the most popular way. Since this colour system, which has been approved by the International Commission, Colorimetry is defined by the Commission Internationale de l'Eclairage (CIE). A colorimeter is a device that measures colour. The tri-stimulus method is used to measure the reflecting colours of surfaces. system. A faint, continuous transition can be seen using the colorimeter. between the first erythematous response and the delayed erythematous response and darkening of skin that is not visible to the naked eye. The intensity vs. wavelength data

(i.e., tristimulus analysis) is converted into three numbers that show how the data was processed. [72-75]

The reflected-light colorimeter can measure five different colour schemes. Skin colour is measured using the L*a*b* system, which is stated in three dimensions: the value of L* (luminance) indicates the relative lightness of a colour, ranging from absolutely black to entirely white. The a* value reflects the colour range from entirely black (L* = 0) to completely white (L* = 100). the proportion of red (positive value) to green (negative value) The b* number shows the balance between yellow and blue. (with a positive value) and blue (with a negative value) . The device has been calibrated. Colorimetry has a wide range of clinical uses, including skin typology, race, anatomical distribution of pigment and photo-protection factors, sunscreens, and depigmentation treatments.[76]

Conclusion:

Vitiligo is one of the serious diseases that has been studied for long time. The process of repigmentation is sluggish and only visible after a few months of treatment. As a result, a sensitive and precise method that can detect even modest variations in depigmentation and/or repigmentation during and after vitiligo treatment is critical for the appropriate assessment of this condition in clinical studies. VASI, the rule of nine and Wood's lamp are likely to be the best techniques available for assessing the degree of pigmentary lesions and measuring the extent and progression of vitiligo in the clinic and in clinical trials.

The development of more convenient diagnostic tools is the main objectives these days especially as we learn more about the pathogenesis of the disease. Patients whose condition is difficult to diagnose, unresponsive to simple topical treatments, or causing psychological distress should be referred to a dermatology unit.

References:

1. Taieb A, Picardo M. The definition and assessment of vitiligo: a consensus report of the Vitiligo Eropean Task Force. Pigment Cell Res 2007; 20: 27–35.
2. AlGhamdi KM. A survey of vitiligo management among dermatologists in Saudi Arabia. J Eur Acad Dermatol Venereol 2009; 23: 1282–1288.
3. Alghamdi KM, Kumar A. Depigmentation therapies for normal skin in vitiligo universalis. J Eur Acad Dermatol Venereol 2011; 25: 749–757.
4. Sehgal VN, Srivastava G. Vitiligo: compendium of clinico-epidemiological features. Indian J Dermatol Venereol Leprol 2007; 73:149–56.
5. Picardo M, Dell'Anna ML, Ezzedine K, Hamzavi I, Harris JE, Parsad D, et al. Vitiligo. Nat Rev Dis Primers. 2015 Jun; 1(1): 15011.
6. Ezzedine K, Lim HW, Suzuki T, Katayama I, Hamzavi I, Lan CC, et al.; Vitiligo Global Issue Consensus Conference Panelists. Revised classification/nomenclature of vitiligo and related issues: the Vitiligo Global Issues Consensus Conference. Pigment Cell Melanoma Res. 2012 May; 25(3):E1–13.
7. Ezzedine K, Grimes PE, Meurant JM, Seneschal J, Leaute-Labreze C, Ballanger F, et al. Living with vitiligo: results from a national survey indicate differences between skin phototypes. BrJ Dermatol. 2015 Aug; 173(2): 607–9.
8. Goh B-K, Pandya AG. Presentations, signs of activity, and differential diagnosis of vitiligo. Dermatol Clin. 2017;35(2):135-144. doi:10.1016/j. det.2016.11.004.
9. Ma J, Cheng L, Wu Y-Y, Cai X-Y, Liang B, Xiao F-L. A retrospective analysis of 925 cases of segmental vitiligo in a Chinese Han population. J Eur Acad Dermatol Venereol. 2021;35(6):e379-e381. doi:10.1111/jdv.17150.
10. Sosa JJ, Currimbhoy SD, Ukoha U, et al. Confetti-like depigmentation: a potential sign of rapidly progressing vitiligo. J Am Acad Dermatol. 2015;73(2):272-275. doi:10.1016/j.jaad.2015.05.014.
11. Nofal A, Fawzy MM, Alakad R. The use of trichloroacetic acid as a depigmenting therapy in universal vitiligo. J Dtsch Dermatol Ges. 2021;19(2):241- 246. doi:10.1111/ddg.14316.
12. Mattoo S, Handa S, Kaur I et al. Psychiatric morbidity in vitiligo and psoriasis: a comparative study from India. J Dermatol 2001; 28:424–32.
13. Balaban €O, Atag€un M, €Ozg€uven H et al. Psychiatric morbidity in patients with vitiligo. Dusunen Adam 2011; 24:306–13 (in Turkish).
14. Karia S, De Sousa A, Shah N et al. Psychiatric morbidity and quality of life in skin diseases: a comparison of alopecia areata and psoriasis. Ind Psychiatry J 2015; 24:125.
15. Howitz J, Brodthagen H, Schwartz M, Thomsen K. Prevalence of vitiligo. Epidemiological survey on the Isle of Bornholm, Denmark. Arch Dermatol. 1977 Jan; 113(1): 47–52.
16. Ezzedine K, Eleftheriadou V, Whitton M, van Geel N. Vitiligo. Lancet. 2015 Jul; 386(9988): 74–84.

17. Alkhateeb A, Fain PR, Thody A, Bennett DC, Spritz RA. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. Pigment Cell Res. 2003 Jun; 16(3): 208–14.
18. Lu T, Gao T, Wang A, Jin Y, Li Q, Li C. Vitiligo prevalence study in Shaanxi Province, China. Int J Dermatol. 2007 Jan; 46(1): 47–51.
19. Behl PN, Bhatia RK. 400 cases of vitiligo. A clinico-therapeutic analysis. Indian J Dermatol. 1972 Jan; 17(2): 51–6.
20. Sehgal VN, Srivastava G. Vitiligo: compendium of clinico-epidemiological features. Indian J Dermatol Venereol Leprol. 2007 May- Jun; 73(3): 149–56.
21. Das SK, Majumder PP, Chakraborty R, Majumdar TK, Haldar B. Studies on vitiligo. I. Epidemiological profile in Calcutta, India. Genet Epidemiol. 1985; 2(1): 71–8.
22. Ezzedine K, Diallo A, Leaute-Labreze C, Seneschal J, Boniface K, Cario-Andre M, et al. Pre- vs. post-pubertal onset of vitiligo: multivariate analysis indicates atopic diathesis association in pre-pubertal onset vitiligo. Br J Dermatol. 2012 Sep; 167(3): 490–5.
23. Nicolaidou E, Antoniou C, Miniati A, Lagogianni E, Matekovits A, Stratigos A, et al. Childhood- and later-onset vitiligo have diverse epidemiologic and clinical characteristics. J Am Acad Dermatol. 2012 Jun; 66(6): 954–8.
24. Lee H, Lee MH, Lee DY, Kang HY, Kim KH, Choi GS, et al. Prevalence of vitiligo and associated comorbidities in Korea. Yonsei Med J. 2015 May; 56(3): 719–25.
25. Le Poole IC, Das PK, van den Wijngaard RM, Bos JD, Westerhof W. Review of the etiopathomechanism of vitiligo: a convergence theory. Exp Dermatol. 1993 Aug; 2(4): 145– 53.
26. Schallreuter KU, Bahadoran P, Picardo M, Slominski A, Elassiuty YE, Kemp EH, et al. Vitiligo pathogenesis: autoimmune disease, genetic defect, excessive reactive oxygen species, calcium imbalance, or what else? Exp Dermatol. 2008 Feb; 17(2): 139–60.
27. Dell'anna ML, Picardo M. A review and a new hypothesis for non-immunological pathogenetic mechanisms in vitiligo. Pigment Cell Res. 2006 Oct; 19(5): 406–11.
28. Rodrigues M, Ezzedine K, Hamzavi I, Pandya AG, Harris JE; Vitiligo Working Group. New discoveries in the pathogenesis and classification of vitiligo. J Am Acad Dermatol. 2017 Jul; 77(1): 1–13.
29. Sandoval-Cruz M, Garcia-Carrasco M, Sanchez- Porras R, Mendoza-Pinto C, Jimenez-Hernandez M, Munguia-Realpozo P, et al. Immunopathogenesis of vitiligo. Autoimmun Rev. 2011 Oct; 10(12): 762–5.
30. Richmond JM, Frisoli ML, Harris JE. Innate immune mechanisms in vitiligo: danger from within. Curr Opin Immunol. 2013 Dec; 25(6): 676–82.
31. Majumder PP, Nordlund JJ, Nath SK. Pattern of familial aggregation of vitiligo. Arch Dermatol. 1993 Aug; 129(8): 994–8.
32. Das SK, Majumder PP, Majumdar TK, Haldar B, Rao DC. Studies on vitiligo. II. Familial aggregation and genetics. Genet Epidemiol. 1985; 2(3): 255–62.
33. Nath SK, Majumder PP, Nordlund JJ. Genetic epidemiology of vitiligo: multilocus recessivity cross-validated. Am J Hum Genet. 1994 Nov; 55(5): 981–90.

34. Spritz RA, Andersen GH. Genetics of Vitiligo. Dermatol Clin. 2017 Apr; 35(2): 245–55.
35. Spritz RA. Modern vitiligo genetics sheds new light on an ancient disease. J Dermatol. 2013 May; 40(5): 310–8.
36. Spritz RA. Shared genetic relationships underlying generalized vitiligo and autoimmune thyroid disease. Thyroid. 2010 Jul; 20(7): 745–
37. Czajkowski R, Męcińska-Jundziłł K. Current aspects of vitiligo genetics. Postepy Dermatol Alergol. 2014 Aug; 31(4): 247–55.
38. Jin Y, Mailloux CM, Gowan K, Riccardi SL, LaBerge G, Bennett DC, et al. NALP1 in vitiligo- associated multiple autoimmune disease. N Engl J Med. 2007 Mar; 356(12): 1216–25.
39. Spritz RA, Hearing VJ Jr. Genetic disorders of pigmentation. Adv Hum Genet. 1994; 22: 1–45.
40. Baharav E, Merimski O, Shoenfeld Y, Zigelman R, Gilbrud B, Yecheskel G, et al. Tyrosinase as an autoantigen in patients with vitiligo. Clin Exp Immunol. 1996 Jul; 105(1): 84–8.
41. Kemp EH, Gawkrodger DJ, Watson PF, Weetman AP. Immunoprecipitation of melanogenic enzyme autoantigens with vitiligo sera: evidence for cross-reactive autoantibodies to tyrosinase and tyrosinase-related protein- 2 (TRP-2). Clin Exp Immunol. 1997 Sep; 109(3): 495–500.
42. Rezaei N, Gavalas NG, Weetman AP, Kemp EH. Autoimmunity as an aetiological factor in vitiligo. J Eur Acad Dermatol Venereol. 2007 Aug; 21(7): 865–76.
43. Maresca V, Roccella M, Roccella F, Camera E, Del Porto G, Passi S, et al. Increased sensitivity to peroxidative agents as a possible pathogenic factor of melanocyte damage in vitiligo. J Invest Dermatol. 1997 Sep; 109(3): 310–3.
44. Jimbow K, Chen H, Park JS, Thomas PD. Increased sensitivity of melanocytes to oxidative stress and abnormal expression of tyrosinaserelated protein in vitiligo. Br J Dermatol. 2001 Jan; 144(1): 55–65.
45. Morrone A, Picardo M, de Luca C, Terminali O, Passi S, Ippolito F. Catecholamines and vitiligo. Pigment Cell Res. 1992 Mar; 5(2): 65–9.
46. Kostyuk VA, Potapovich AI, Cesareo E, Brescia S, Guerra L, Valacchi G, et al. Dysfunction of glutathione S-transferase leads to excess 4-hydroxy-2-nonenal and H(2) O(2) and impaired cytokine pattern in cultured keratinocytes and blood of vitiligo patients. Antioxid Redox Signal. 2010 Sep; 13(5): 607–20.
47. Ozturk IC, Batcioglu K, Karatas F, Hazneci E, Genc M. Comparison of plasma malondialdehyde, glutathione, glutathione peroxidase, hydroxyproline and selenium levels in patients with vitiligo and healthy controls. Indian J Dermatol. 2008; 53(3): 106–10.
48. Dell'Anna ML, Ottaviani M, Albanesi V, Vidolin AP, Leone G, Ferraro C, et al. Membrane lipid alterations as a possible basis for melanocyte degeneration in vitiligo. J Invest Dermatol. 2007 May; 127(5): 1226–33.
49. Bickers DR, Athar M. Oxidative stress in the pathogenesis of skin disease. J Invest Dermatol. 2006 Dec; 126(12): 2565–75.

50. van den Boorn JG, Picavet DI, van Swieten PF, van Veen HA, Konijnenberg D, van Veelen PA, et al. Skin-depigmenting agent monobenzone induces potent T-cell autoimmunity toward pigmented cells by tyrosinase haptenation and melanosome autophagy. J Invest Dermatol. 2011 Jun; 131(6): 1240–51.
51. Yu R, Broady R, Huang Y, Wang Y, Yu J, Gao M, et al. Transcriptome analysis reveals markers of aberrantly activated innate immunity in vitiligo lesional and non-lesional skin. PLoS One. 2012; 7(12):e51040.
52. Jin, Ying, et al. "NALP1 in vitiligo-associated multiple autoimmune disease." New England Journal of Medicine 356.12 (2007): 1216-1225..
53. Thulasingam S, Massilamany C, Gangaplara A, Dai H, Yarbaeva S, Subramaniam S, et al. miR-27b*, an oxidative stress-responsive microRNA modulates nuclear factor-kB pathway in RAW 264.7 cells. Mol Cell Biochem. 2011 Jun; 352(1-2): 181–8.
54. Naughton GK, Eisinger M, Bystryn JC. Detection of antibodies to melanocytes in vitiligo by specific immunoprecipitation. J Invest Dermatol. 1983 Dec; 81(6): 540–2.
55. Norris DA, Kissinger RM, Naughton GM, Bystryn JC. Evidence for immunologic mechanisms in human vitiligo: patients' sera induce damage to human melanocytes in vitro by complement-mediated damage and antibody-dependent cellular cytotoxicity. J Invest Dermatol. 1988 Jun; 90(6): 783–9.
56. Ongenae K, Van Geel N, Naeyaert JM. Evidence for an autoimmune pathogenesis of vitiligo. Pigment Cell Res. 2003 Apr; 16(2): 90–100.
57. Ogg GS, Rod Dunbar P, Romero P, Chen JL, Cerundolo V. High frequency of skin-homing melanocyte-specific cytotoxic T lymphocytes in autoimmune vitiligo. J Exp Med. 1998 Sep; 188(6): 1203–8.
58. Duteil L. Objective methods to assess pigmentation. In Ortonne JP, Ballotti R, eds. Mechanism of Suntanning. Martin Dunitz, London, 2002.
59. Agache P. Skin color measurement in measuring the skin. In Agache P, Humbert P, eds. Measuring the Skin. Springer, Berlin, Germany, 2004: 33–39.
60. Van Geel NAC, Ongenae K, Vander Haeghen YMSJ, Naeyaert JM. Autologous transplantation technique for vitiligo: how to evaluate treatment outcome. Eur J Dermatol 2004; 14: 46–51.
61. Aspres N, Egerton IB, Lim AC et al. Imagin the skin. Austrralas J Dermatol 2003; 44: 19 27.
62. Ardigo M, Muzio F, Picardo M, Brazzelli V. Non-invasive methods for vitiligo evaluation. In Picardo M, Taieb A, eds. Vitiligo. Springer-Verlag, Berlin Heidelberg, 2010: 183–195.
63. Paraskevas LR, Halpern AC, Marghoob AA. Utility of the Wood's light: five cases from a pigmented lesion clinic. Br J Dermatol 2005; 152: 1039–1044.
64. Gawkrodger DJ, Ormerod AD, Shaw L et al. Guideline for the diagnosis and management of vitiligo. Br J Dermatol 2008; 159: 1051–1076.
65. Bhor U, Pande S. Scoring systems in dermatology. Indian J Dermatol
66. Venereol Leprol 2006; 72: 315–321.

67. Njoo MD, Das PK, Bos JD, Westerhof W. Association of the Ko¨bner phenomenon with disease activity and therapeutic responsiveness in vitiligo vulgaris. Arch Dermatol 1999; 135: 407–413.
68. Hamzavi I, Jain H, McLean D et al. Parametric modeling of narrowband UV-B phototherapy for vitiligo using a novel quantitative tool: the Vitiligo Area Scoring Index. Arch Dermatol 2004; 140: 677–683.
69. Tuzun Y, Yazici H. A method of measuring skin lesions. Arch Dermatol 1981; 117: 192.
70. Aydin F, Senturk N, Sahin B et al. A practical method for the estimation of vitiligo surface area: a comparison between the point counting and digital plainmetry techniques. Eur J Dermatol 2007; 17: 30–32.
71. Marrakchi S, Bouassida S, Meziou TJ et al. An objective method for the assessment of vitiligo treatment. Pigment Cell Melanoma Res 2008; 21: 106–107.
72. Seitz JC, Whitmore CG. Measurements of erythema and tanning responses in human skin using a tristimulus colorimeter. Dermatologica 1988; 177: 70–75.
73. Westerhof W, Van Hasselt BAAM, Kammeijer A. Quantification of UV-induced erythema with a portable computer controlled chromameter. Photodermatol 1986; 3: 310–314.
74. Serup J, Agner T. Colorimetric quantification of erythema – a comparison of two colorimeters (Lange Micro Color and Minolta Chroma Meter CR-200) with a clinical scoring scheme and laser-Doppler flowmetry. Clin Exp Dermatol 1990; 15: 267–272.
75. Queille-Roussel C, Poncet M, Scarffer H. Quantification of skin color changes induced by topical corticosteroid preparation using the Minolta Chroma Meter. Br J Dermatol 1991; 124: 264–270.
76. Park SB, Suh DH, Youn JI. A long-term course of colorimetric evaluation of ultraviolet light-induced skin reactions. Cli Exp Dermatol 1999; 24: 315–320.