Journal of Pharmaceutical Research International

33(42B): 389-396, 2021; Article no.JPRI.73245
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

An Overview on the Epidemiology, Pathophysiology and Treatment of Vitiligo: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i42B32456
Editor(s):
(1) Dr. Sawadogo Wamtinga Richard, Ministry of Higher Education, Scientific Research and Innovation, Burkina Faso.
Reviewers:
(1) Yohanes Firmansyah, Tarumanagara University, Indonesia.
(2) Nabeel K. Alhamzawi, Diwaniyah Teaching Hospital, Iraq.
Complete Peer review History: https://www.sdiarticle4.com/review-history/73245

Review Article

Received 22 June 2021
Accepted 30 August 2021
Published 03 September 2021

ABSTRACT

Vitiligo is one of the complex diseases that has existed during the entire history of humanity and so far we have not fully understood it, serval theories have been proposed most of them suggest strong linkage between deficiencies in certain genes and the disease, refereeing that the disease has strong genetic factor that plays a rule in triggering the disease, and the epidemiology studies confirms also that theory due to higher incidence in people who have siblings but this theory does not fully unlocks the full causes of the disease as it seems also to have strong environmental triggers. One of the biggest problem about the disease and the QoL is not the disease lifestyle itself but rather the social and psychological effects of the disease and the social acceptance impact, because it affects the appearance of its patients and thus affects their social acceptance leading to some serious psychological and depressive disorders, and that effects differs from society to another and by different categories, that's why psychological follow up and treatment is critical part of the overall treatment. In this review, we overview recent updates in epidemiology, pathophysiology and treatment of vitiligo.

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Keywords: Epidemiology; pathophysiology; vitiligo.

1. INTRODUCTION

Vitiligo is a common acquired skin condition that comes from the loss of melanocytes in the epidermis and shows up on the body as well-defined white areas. There are several hypotheses on how vitiligo develops, but the actual cause is still unknown. It's a type of autoimmune condition [1].

Vitiligo is a terrible autoimmune condition that has a detrimental impact on sufferers' self-esteem and quality of life. Existing vitiligo treatments are non-targeted immuno-suppressants that have only limited efficacy when administered and most commonly used off-label [2,3,4]. Furthermore, vitiligo with an early onset is linked to a more severe condition.

Because a causal (gene) treatment is not (yet) available, current techniques focus on halting progression and attaining repigmentation in order to correct the morphological and functional inadequacies of depigmented skin areas [5].

2. EPIDEMIOLOGY

The most prevalent cause of depigmentation is vitiligo. It can strike at any age, from childhood to adulthood, but it is most common in the second and third decades. The onset age differs between the sexes in most cases. It affects people of all ethnicities equally and affects 0.1 percent to 2% of people worldwide, including adults and children [1,6]. Vitiligo is predicted to be present in 0.093 percent of Chinese people, 0.34 percent on Martinique's island, 0.38 percent in Denmark, 1% in the United States, and 0.5 percent to 1.13 percent in India [7-13].

In a study Vitiligo was shown to have a significant prevalence in Africa and in female patients. In recent years, the prevalence has remained stable. In both population- or community-based research and hospital-based studies, it demonstrated an inverse tendency with increasing age [14]. In hospital-based research, vitiligo was shown to be as common as 2.5 percent (1.6 percent, 3.4 percent) in Africa, 1.6 percent (1.1 percent, 2.0 percent) in Asia, and 1.5 percent (0.1 percent, 3.1 percent) in America [14].

3. SOCIAL AND PSYCHOLOGICAL EFFECTS

Skin problems that alter one's appearance can have a significant impact on one's job, as well as personal and social interactions. This impact on self-esteem and beauty perception is independent of race, age, gender, or socioeconomic background [15].

Vitiligo is a disfiguring and stigmatising disorder that can cause major psychologic problems in everyday life. It affects roughly 0.5 percent of the world's population, and it affects both males and females equally [5].

Pigmentation is sometimes viewed as a passport to society in societies that have a cultural predilection for specific skin tones, and perceived flaws can be catastrophic [15]. Patients with low self-esteem also dealt badly with the sickness, whereas those with strong self-esteem did better, according to studies. Following research have repeatedly shown that vitiligo has a negative impact on patients' self-esteem and quality of life (QoL). Isolation, stigmatisation, loss of self-esteem, melancholy, and self-consciousness are all symptoms of vitiligo [15].

4. CHILDREN WITH VITILIGO

Vitiligo affects between 25 and 38 percent of children. in a study The quality of life of 50 children with vitiligo was compared to the quality of life of 50 children with atopic dermatitis and healthy controls who were age and sex matched. When compared to healthy controls, patients with vitiligo had considerably higher Dermatology Life Quality Index values [15,16].

However in another study done online found that vitiligo had a detrimental impact on CDLQI values. The face and legs were the most irritating areas for both youngsters and their parents. A BSA of more than 25% was linked to feelings of self-consciousness, dread, and bullying. Teenagers between the ages of 15 and 17 were the most self-conscious of all the paediatric age groups [15,17].

Vitiligo has also been connected to serious depression. Dark-skinned people had a higher rate of social phobia, a higher risk of suicide, and poorer self-esteem than lighter-skinned people.

People with lighter skin had a higher quality of life. Vitiligo lesions are linked to an increased risk of major depressive illness and social anxiety, as well as a lower quality of life and self-esteem [18].

So overall according to studies, that have been done on the different demographics that have the disease and how they coup with i. specific demographics of vitiligo sufferers are more likely to have low acceptance and quality of life. As a result, it's safe to assume that these patients will require more intensive treatment. As a result, it appears that psychological therapies are critical in patients who have a lower quality of life [19].

4.1 Etiology

The illness is frequently connected with a few autoimmune disorders, the most prevalent of which is thyroid problems. The cause of vitiligo is unknown, but various theories exist to explain its pathology [1].

4.2 Genetically

It seems like there's some genetic factors that play also a role in determining whether a person will suffer vitiligo or not, A vitiligo patient's sibling has a 6% chance of getting the condition, whereas an identical twin has a 23% chance [2]. A study of 160 American Caucasian families found that vitiligo runs in families, with 20% of those affected having at least one first-degree relative with the disease [7]. Furthermore, patients with vitiligo and their family are more likely to acquire additional autoimmune disorders such as autoimmune thyroiditis, type 1 diabetes, pernicious anaemia, and Addison's disease, implying that vitiligo is an autoimmune disease. [2], A few genes, including DDR1, XBP1, and NLRP1, have been reliably and functionally linked to the disease in this setting. [7] and also In addition to the genes indicated above, markers for ACE, AIRE, CD4, COX2, ESR1, EDN1, FAS, FOXD3, FOXP3, IL1 - RN, IL-10, MBL2, MC1R, MYG1, Nrf2, PDGFRA, PRO2268, SCF, SCGF, TXNDC5, UVRAG, and VDR genes were discovered to be associated with vitiligo symptoms, but these connections we not found in another different communities, or populations. [7] in other studies suggested that Single nucleotide polymorphisms (SNPs) in one of these possible genes that is associated with the disease (Forkhead box D3-FOXD3) are found on chromosome 1p31.3-32.2. A second possible gene is NACHT-LRR-PYD-containing protein 1 (NALP1), which is found on chromosome 17p13 [20].

UVRAG (ultraviolet radiation resistance-associated gene) is a photoprotection gene that also has a function in autophagy. UVRAG had two SNPs that were substantially different in 439 controls and 225 NSV patients [21,22,23]. Vitiligo has been linked to HLA-DRB1*07, HLA-A2, 11, 28, 31, 33, HLA-B17, 35, 40, and 44 in studies [21,24,25].

4.3 Environmental

Multiple studies suggest that a combination of innate melanocyte abnormalities and exposure to particular environmental variables may play a key role in disease progression. This was demonstrated in a group of manufacturing workers who acquired vitiligo after being exposed to monobenzone, a phenolic organic compound. Other phenolic and catecholic compounds present in dyes (particularly hair dyes), resins/adhesives, and leather were linked to vitiligo in later investigations [2,26,27,28].

4.4 Pathophysiology

Until date, the pathophysiology of vitiligo has remained a mystery, and various explanations have been offered. [7] A variety of hypotheses have been proposed to explain the pathophysiology of vitiligo. Innervation, microvascular anomalies, oxidative stress-induced melanocyte degeneration, problems in melanocyte adhesion, autoimmune, somatic mosaicism, and genetic factors are all included in these hypotheses [29-36]. The autoimmune hypothesis is presently the most commonly cited and researched among professionals. [7] Biochemical/cytotoxic, neurological, and autoimmune are three prominent explanations for the pathophysiology of vitiligo that are not mutually incompatible. Recent research suggests that vitiligo is caused by an autoimmune response [37].

Environmental stressors like as UV radiation and various chemicals, which can enhance the generation of reactive oxygen species, are constantly exposed to epidermal cells, including melanocytes (ROS). While healthy melanocytes can withstand these stresses, vitiligo patients' melanocytes appear to be more sensitive [2].

Autoimmunity is thought to play a role in the pathophysiology of vitiligo for a long time. The

CD8+ cytotoxic T-cells are the major culprits. The presence of epidermotropic cutaneous lymphocyte antigen positive lymphocytes with an elevated CD8+/CD4+ ratio in perilesional skin biopsies supports the function of cytotoxic T-cells in the aetiology of vitiligo. In individuals with aggressively spreading lesions, these T-cells have been found to cause degenerative alterations in melanocytes and vacuolization of basal cells in the normal-appearing perilesional skin. These T-cells have higher levels of CD25 and MHC II (particularly HLA-DR) expression as well as the ability to release interferon gamma (IFN), which leads to increased expression of intercellular adhesion molecule-1 and, as a result, enhanced T-cell migration to the skin, creating a vicious cycle [38].

Interferon (IFN) has recently been discovered as a component of the 'signature cytokine profile' linked to vitiligoaetiology. Harris and colleagues discovered that IFNs play a key role in the spread of vitiligo lesions in an engineered mouse model of vitiligo by increasing the production of CXCL10, which then regulates CD8+ T-cell invasion of epidermal and follicular tissues [38,39].

Antibodies against cell surface pigment cell antigens, intracellular pigment cell antigens, and non-pigment cell antigens are seen in vitiligo patients, and they are divided into three categories. Certain antigens, such as VIT 40/75/90, have been found in 83 percent of vitiligo patients. Patients with vitiligo have been reported to have non-specific antibodies against certain antigens. Because melanocytes are far more vulnerable to immune-mediated injury, even minor damage from non-specific antibodies is likely to cause deadly harm to melanocytes but not to surrounding cells [38].

Toxic metabolites: both intracellular and extracellular, such as phenols or quinones, can accumulate and destroy melanocytes in genetically sensitive individuals, resulting in autocytotoxic injury. Tyrosine has been demonstrated to produce certain electrically unstable by-products when it enters the melaninogenic pathways, which have the ability to damage other cellular substrates, resulting in melanocyte death [38].

Neurogenic Theory: For many years, SV was thought to have a dermatomal distribution, which raised the possibility of neurogenic mechanisms being involved. There have been several reports of encephalitis preceding SV. Nonetheless, neuropeptides regulate regional skin immunity, and some of them [such as melanocyte-stimulating hormone (-MSH)] have essential impacts on melanocytes. There were two examples of SV patients with schwannomas discovered. Given their similar neural crest origin, this is more of a hint toward somatic mosaicism than an explanation for a neurogenic source of SV.in a study done on patients with SV indicated that the lesional side of the body had a slower nerve conduction velocity than the contralateral side, which was more prominent in stable SV patients. If these findings are verified, they could provide insight on the neurogenic involvement in SV, despite the slight variation [40].

Types: There are 2 main types according to spreadability of the disease into generalized vitiligo (GV) or focal vitiligo (FV):

1. Generalized vitiligo it can be divided into: Acrofacial, Vulgaris, Universalis, Mixed
2. Localisedvitiligo which can be divided into Focal, Segmental, Mucosal [21].

The description of these types as follows:

- Macules form in many sites on the body in **Generalized**, which is the most frequent type.
- **Segmental** refers to a condition that affects only one side of the body or a specific location, such as the hands or face.
- **Mucosal**, which affects the mouth and/or genital mucous membranes.
- **Focal**, a rare kind in which the macules are concentrated in a limited area and do not spread in a predictable pattern over the course of one to two years.
- **Trichome** signifies that there is a white or colourlesscentre, followed by a lighter pigmented area, and finally a normal-colored area.
- **Universal vitiligo** is a rare kind of vitiligo in which more than 80% of the body's skin is devoid of colour [41].

Diagnosis: Vitiligo manifests clinically as white spots on the body that are symmetrically distributed and more visible in those with dark complexion. The lesions are characterised by well-demarcated pearly white or depigmented macules and patches that are oval, round, or linear in shape, have convex borders, and range

in size from a few millimetres to centimetres [1]. Furthermore, vitiligo with an early onset is linked to a more severe condition [7].

Trichrome, Marginal inflammatory, and Quadrichromevitiligo are the three clinical types of vitiligo [1].

A common clinical symptom is the Koebner phenomenon (the development of vitiligo at specific trauma-prone areas, such as a cut, burn, or abrasion). The hands, forearms, feet, and face are the most common sites for first lesions, with a periocular or perioral distribution being the most common [1,42,43].

Treatment: The current therapy approaches are aimed at slowing the disease's progression and attaining re-pigmentation. Corticosteroids, topical immunomodulators, photo (chemo) therapy, surgery, combination therapies, and depigmentation of normally pigmented skin are some of the treatments available. Traditional Chinese medicine appears to be more successful than the modern vitiligo treatment [24].

Therapy should target cellular targets starting with overlapping pathological mechanisms. [20] In adults, dexamethasone 10 mg divided in two days as pulse treatment has been shown to stop fast progressing vitiligo while generating less side effects than the continuous regimen. Topical immunomodulators (TIMS) have an anti-inflammatory and anti-differentiation effect. Tacrolimus has been shown to give good re-pigmentation when used in conjunction with occlusion (hydrocolloid dressing) [20].

Many therapies have been utilized for a long time; however, some novel advances include narrowband ultraviolet (UV) B (311 nm) therapy, the combination of corticosteroid cream + UVA therapy, and autologous pigment cell transplantation in various modalities. Depigmentation chemicals can be used to eliminate leftover pigment in cases of extensive vitiligo. Sunscreens and camouflage products may aid in the patient's disease management [5].

The Cellular-Oriented Treatment: Both tacrolimus and pimecrolimus can influence T cell maturation and activation, as well as melanocyte and melanoblast migration. This last TIM feature may thus influence the differentiation process, which is likely hindered in vitiligo. Currently, tacrolimus ointment is provided as a 0.1% cream applied for at least 10 weeks [20] also A well-balanced antioxidant pool is preferable to a single-molecule antioxidant pool. It should be taken orally during the reactivation stages and as a supplement to phototherapies [20].

Phototherapy: It's the gold standard therapy, to the best of our knowledge. UVA, BB-UVB, NB-UVB, and excimer are among the sources accessible. The majority of NB-UVB trials were able to achieve re-pigmentation rates of up to 70%. The initial exposure could be 70 percent of the MED (minimum erythema dose) or a fixed absolute value (100-280 mJ/cm 2). The duration of treatment varies between 6 and 12 months [20].

According to studies longer treatment durations should be encouraged to improve treatment response, and phototherapy responsiveness should be assessed for at least 6 months. NBUVB phototherapy had a greater overall treatment response than PUVA therapy. The face and neck are expected to have the most effective response, while the hands and feet will have the least effective response [44].

Stem cell therapy for vitiligo: Mesenchymal stem cell (MSC)-based therapy involving autologous and allogenic MSCs shows great promise in treating many conditions. CSCs promote wound healing, and they can differentiate into multiple cell lineages, including keratinocytes. Therefore, MSCs can be used to treat congenital or acquired skin defects. Because of their immunomodulatory properties, CSCs may be useful in treating inflammatory and autoimmune skin diseases. In particular, CSCs may be effective in treating large vitiligo lesions such as immunosuppressants or transplanted grafts. Cancer stem cells can also be a new cell source for hair regeneration in the treatment of cicatricial alopecia and androgenetic alopecia [45].

The presence of stem cells in the skin lesions capable of self-renewal and differentiation into melanocytes gives new hope to vitiligo patients suffering from a lesion on shiny skin. However, the re-pigmentation of the lustrous lesions of the skin is very difficult and rare with the current treatments available. This clearly means that the treatments available so far are not effective enough to activate the differentiation and transmigration of dermal stem cells into the epidermis of the lesion. Stimulating these stem cells to differentiate into melanocytes and migrate into the lesional epidermis could

be ideal for re-pigmentation of excised lesions [46].

5. CONCLUSION

Vitiligo is one of the complex diseases that has existed during the entire history of humanity. Serval treatments are being used currently to treat the disease, pharmacological treatment includes mostly off label use of the anti-autoimmune disease drugs, however there are better treatment that are being improved and used, one of which is phototherapy which seems the golden standard for the therapy, overall longer treatment plans should be considered to have higher responses, according to some studies NBUVB phototherapy had a greater overall treatment response than PUVA therapy.Psychological follow up and treatment is critical part of the overall treatment.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Ahmed jan N, Masood S. Vitiligo. [Updated 2020 Aug 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021. Available:https://www.ncbi.nlm.nih.gov/books/NBK559149/
2. Rashighi M, Harris JE. Vitiligo Pathogenesis and Emerging Treatments. Dermatol Clin. 2017;35(2):257-265. DOI: 10.1016/j.det.2016.11.014. PMID: 28317534; PMCID: PMC5362109.
3. Vitiligo. Ezzedine K, Eleftheriadou V, Whitton M, van GeelN. Lancet. 2015; 386(9988):74-84.
4. Dell'Anna MLEK, Hamzavi I, Harris J, Parsad D, Taieb A, Picardo M. Vitiligo. Nature Reviews Disease Primers. 2015; 1(1):1–16.
5. Njoo MD, Westerhof W. Vitiligo. Pathogenesis and treatment. Am J Clin Dermatol. 2001;2(3):167-81. DOI: 10.2165/00128071-200102030-00006. PMID: 11705094.
6. Bergqvist C, Ezzedine K. Vitiligo: A Review. Dermatology. 2020;236(6):571-592.
7. Tarlé RG, Nascimento LM, Mira MT, Castro CC. Vitiligo--part 1. An Bras Dermatol. 2014;89(3):461-70. DOI: 10.1590/abd1806-4841.20142573. PMID: 24937821; PMCID: PMC4056705.
8. Studies on vitiligo. I. Epidemiological profile in Calcutta, India. Das SK, Majumder PP, Chakraborty R, Majumdar TK, Haldar B Genet Epidemiol. 1985; 2(1):71-8.
9. Lu T, Gao T, Wang A, Jin Y, Li Q, Li C. Vitiligo prevalence study in Shaanxi Province, China. Int J Dermatol. 2007;46: 47–51.
10. Boisseau-Garsaud AM, Garsaud P, Cales-Quist D, Helenon R, Queneherve C, Claire RC. Epidemiology of vitiligo in the French West Indies (Isle of Martinique) Int J Dermatol. 2000;39:18–20.
11. Howitz J, Brodthagen H, Schwartz M, Thomsen K. Prevalence of vitiligo. Epidemiological survey on the Isle of Bornholm, Denmark. Arch Dermatol. 1977; 113:47–52.
12. Lerner AB. Vitiligo. Part 2J Invest Dermatol. 1959;32(2):285–310.
13. Mehta NR, Shah KC, Theodore C, Vyas VP, Patel AB. Epidemiological study of vitiligo in Surat area, South Gujarat. Indian J Med Res. 1973;61:145–154.
14. Zhang Y, Cai Y, Shi M, Jiang S, Cui S, Wu Y, Gao XH, Chen HD. The Prevalence of Vitiligo: A Meta-Analysis. PLoS One. 2016;11(9):e0163806. DOI: 10.1371/journal.pone.0163806. PMID: 27673680; PMCID: PMC5038943.
15. Grimes PE, Miller MM. Vitiligo: Patient stories, self-esteem, and the psychological burden of disease. Int J WomensDermatol. 2018;4(1):32-37. DOI: 10.1016/j.ijwd.2017.11.005. PMID: 29872674; PMCID: PMC5986114.
16. Boza JC, Giongo N, Machado P, Horn R, Fabbrin A, Cestari T. Quality of life impairment in children and adults with vitiligo: a cross-sectional study based on dermatology-specific and disease-specific

quality of life instruments. Dermatology. 2016;232(5):619–625.
17. Silverberg J.I., Silverberg N.B. Association between vitiligo extent and distribution and quality-of-life impairment. JAMA Dermatol. 2013;149(2):159–164
18. Ramakrishna P, Rajni T. Psychiatric morbidity and quality of life in vitiligo patients. Indian J Psychol Med. 2014; 36(3):302-3. Erratum in: Indian J Psychol Med. 2015;37(1):111.
DOI: 10.4103/0253-7176.135385.
PMID: 25035556; PMCID: PMC4100418.
19. Bidaki R, Majidi N, MoghadamAhmadi A, Bakhshi H, Sadr Mohammadi R, Mostafavi SA, KazemiArababadi M, Hadavi M, Mirzaei A. Vitiligo and social acceptance. ClinCosmetInvestig Dermatol. 2018; 11:383-386.
DOI: 10.2147/CCID.S151114.
PMID: 30046249; PMCID: PMC6054323.
20. Boissy RE, Dell'Anna ML, Picardo M. On the pathophysiology of vitiligo: possible treatment options. Indian J Dermatol Venereol Leprol. 2012;78(1):24-9.
DOI: 10.4103/0378-6323.90943.
PMID: 22199057.
21. Mohammed GF, Gomaa AH, Al-Dhubaibi MS. Highlights in pathogenesis of vitiligo. World J Clin Cases. 2015;3(3):221-30.
DOI: 10.12998/wjcc.v3.i3.221.
PMID: 25789295; PMCID: PMC4360494.
22. Autophagic and tumour suppressor activity of a novel Beclin1-binding protein UVRAG. Liang C, Feng P, Ku B, Dotan I, Canaani D, Oh BH, Jung JU Nat Cell Biol. 2006; 8(7):688-99.
23. Association of UVRAG polymorphisms with susceptibility to non-segmental vitiligo in a Korean sample. Jeong TJ, Shin MK, Uhm YK, Kim HJ, Chung JH, Lee MH Exp Dermatol. 2010;19(8):e323-5.
24. Comparisons of clinical features of HLA-DRB1*07 positive and negative vitiligo patients in Chinese Han population. Hu DY, Ren YQ, Zhu KJ, Lv YM, Cheng H, Zhang Z, Li Y, He SM, Tang J, Liu JL, Lin Y, Sun YY, ZuoXB, Chen G, Sun LD, Yang S, Zhang XJ. J Eur Acad Dermatol Venereol. 2011;25(11):1299-303.
25. Comparative case control study of clinical features and human leukocyte antigen susceptibility between familial and nonfamilial vitiligo. Misri R, Khopkar U, Shankarkumar U, Ghosh K Indian J Dermatol Venereol Leprol. 2009;75(6): 583-7.
26. Oliver E, Schwartz L, Warren L. Occupational leukoderma preliminary report. JAMA. 1939;113:927–928.
27. Differential diagnosis of idiopathic vitiligo. Part III: Occupational leukoderma. Fisher AA Cutis. 1994;53(6):278-80.
28. Use of permanent hair dyes and risk of vitiligo in women. Wu S, Li WQ, Cho E, Harris JE, Speizer F, Qureshi AA Pigment Cell Melanoma Res. 2015;28(6):744-6.
29. Katz EL, Harris JE. Translational Research in Vitiligo. Front Immunol. 2021;12:624517.
DOI: 10.3389/fimmu.2021.624517.
PMID: 33737930; PMCID: PMC7962476.
30. Vitiligo: Mechanisms of Pathogenesis and Treatment. Frisoli ML, Essien K, Harris JE Annu Rev Immunol. 2020;38:621-648.
31. Segmental vitiligo as the possible expression of cutaneous somatic mosaicism: implications for common non-segmental vitiligo. Taïeb A, Morice-Picard F, Jouary T, Ezzedine K, Cario-André M, Gauthier Y Pigment Cell Melanoma Res. 2008;21(6):646-52.
32. Van Geel N, Speeckaert R, Melsens E, Toelle SP, Speeckaert M, De Schepper S, et al. The distribution pattern of segmental vitiligo: Clues for somatic mosaicism. Br J Dermatol. 2013;168(1):56–64.
DOI: 10.1111/bjd.12013
33. vanGeel N, Mollet I, Brochez L, Dutré M, De Schepper S, Verhaeghe E, et al. . New insights in segmental vitiligo: case report and review of theories. Br J Dermatol. 2012;166:240–6.
DOI: 10.1111/j.1365-2133.2011.10650.x
34. Westerhof W, d'Ischia M. Vitiligo puzzle: the pieces fall in place. Pigment Cell Res. 2007;20(5):345–59.
DOI: 10.1111/j.1600-0749.2007.00399.x
35. Gauthier Y, Andre MC, Taïeb A. A critical appraisal of vitiligo etiologic theories. Is melanocyte loss a melanocytorrhagy? Pigment Cell Res. 2003;16(4):322–32.
DOI: 10.1034/j.1600-0749.2003.00070.x
36. Speeckaert R, Dugardin J, Lambert J, Lapeere H, Verhaeghe E, Speeckaert MM, et al. . Critical appraisal of the oxidative stress pathway in vitiligo: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2018;32(7):1089–98.
DOI: 10.1111/jdv.14792
37. Ghafourian A, Ghafourian S, Sadeghifard N, Mohebi R, Shokoohini Y, Nezamoleslami S, Hamat RA. Vitiligo: symptoms, pathogenesis and treatment.

Int J Immunopathol Pharmacol. 2014; 27(4):485-9.
DOI: 10.1177/039463201402700403.
PMID: 25572727.

38. Amanjot K Arora, Muthu S Kumaran; Pathogenesis of vitiligo: An update. 2017;4(2):65-77.
39. Harris JE, Harris TH, Weninger W, Wherry EJ, Hunter CA, Turka LA et al. A mouse model of vitiligo with focused epidermal depigmentation requires IFN-g for autoreactive CD8+ T-cell accumulation in the skin. J Invest Dermatol. 2012;132: 1869-76.
40. Speeckaert Reinhart, Lambert Jo, BulatVedrana, Belpaire Arno, SpeeckaertMarijn, van GeelNanja, Autoimmunity in Segmental Vitiligo. 2020;11:2819.
Available:https://www.frontiersin.org/article/10.3389/fimmu.2020.568447
41. Cleveland Clinic, Overview, Vitiligo, Symptoms and Causes Diagnosis and Tests Management and Treatment Prevention Outlook / Prognosis Living With Resources.
42. Eleftheriadou V. Reliability and validity of the Vitiligo Signs of Activity Score. Br J Dermatol. 2020;183(5):801-802.
43. De Baat C, Phoa KH, Zweers PGMA, Bolling MC, Rozema FR, Vissink A. Medicaments and oral healthcare. Hyperpigmentation of oral soft tissues due to afamelanotide. Ned Tijdschr Tandheelkd. 2020;127(4):237-243.
44. Bae JM, Jung HM, Hong BY, et al. Phototherapy for Vitiligo: A Systematic Review and Meta-analysis. JAMA Dermatol. 2017;153(7):666–674.
DOI: 10.1001/jamadermatol.2017.0002
45. Toshio Hasegawa, Shigaku Ikeda. Mesenchymal stem cells for the treatment of skin diseases [J]. AIMS Cell and Tissue Engineering. 2017;1(2):104-117.
DOI: 10.3934/celltissue.2017.2.104
46. European Academy of Dermatology and Venereology; 2016.

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Peer-review history:
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