Online ISSN 2623-2723
Print ISSN: 2338-0373

https://doi.org/10.33508/jwm.v9i1.4230

CORRELATION OF SERUM ZINC LEVELS WITH SEVERITY AND DISEASE ACTIVITY IN VITILIGO PATIENTS AT SANJIWANI GIANYAR HOSPITAL

Sayu Widiawati[1], Made Budiani[1] Pradnya Iswara W[2]

ABSTRACT

Vitiligo is an autoimmune disease characterized by well-defined milky-white macule caused by destruction of melanocytes selectively. Management of vitiligo is still challenging due to the pathogenesis is not yet fully understood, and vitiligo can be caused significant psychological distress to patients. Several studies reveal the role of zinc as an important element in the prevention and treatment of vitiligo based on zinc's function as an antiapoptotic, as a bull against free radicals, and as an important element in melanogenesis by stimulating cell-mediated immunity activity, zinc, andalpha-melanocyte stimulating hormone. We conducted an analytical cross-sectional study to determine the correlation between plasma zinc levels and the severity of vitiligo using the VASI score and vitiligo disease activity calculated based on the VIDA score. The results showed that there was a strong negative correlation between serum zinc levels and the VASI score, with a correlation coefficient (r)= -0.668 and p <0.05, and there was a negative correlation between serum zinc levels and the VIDA score with a correlation coefficient (r) = -0.342 and p < 0.05.

***Keywords**: Vitiligo, VASI, VIDA, Zinc Serum.*

ABSTRAK

Vitiligo merupakan penyakit autoimun yang ditandai makula depigmentasi akibat kerusakan melanosit secara selektif. Patogenesis vitiligo belum diketahui secara pasti, hasil pengobatannya yang kurang memuaskan, stigma dan dampak psikologis yang ditimbulkan, menyebabkan vitiligo masih merupakan masalah kesehatan hingga saat ini. Beberapa penelitian sebelumnya menunjukkan peran zinc sebagai elemen penting dalam pencegahan dan pengobatan vitiligo berdasarkan fungsinya sebagai antiapoptosis, antioksidan atau benteng melawan radikal bebas, dan sebagai elemen penting dalam melanogenesis, dengan merangsang aktivitas *cell mediated immunity*, dan merangsang pembentukan *alpha melanocyte stimulating hormone*, oleh karena itu zinc dapat sebagai terapi yang efektif pada vitiligo. Penelitian *cross sectional* yang menghubungkan kadar Zinc serum dengan derajat keparahan vitiligo berdasarkan *Vitiligo Area Scoring Index* (VASI *Score*) dan aktivitas penyakit berdasarkan

Vitiligo Disease Activity Score (VIDA Score) di RSUD Sanjiwani Gianyar menunjukkan terdapat korelasi negatif kuat antara kadar Zinc serum dengan VASI score, dengan koefesien korelasi atau r = - 0,668 dan p < 0,05 dan terdapat korelasi negatif antara kadar zinc serum dengan VIDA score dengan koefisien korelasi (r) = -0,342 dan p < 0,05.

Kata Kunci: Vitiligo, VASI, VIDA, Zinc Serum

---

1. *Department of Dermatology, Sanjiwani Regional General Hospital, Gianyar, Bali, Indonesia. Email sayuwidiawati@gmail.com. / phone +62 821-4473-3849*
2. *Internship Doctor in RS Balimed Denpasar, Bali, Indonesia*.

BACKGROUND

Vitiligo is a universal disease that can occur in all parts of the world and is still a problem in the field of dermatology today. Alikhan et al. define vitiligo as an acquired disorder that affects the skin and mucosa in the form of well-defined depigmented macules due to selective damage to melanocytes.[1]

Traditional vitiligo therapies can control the disease, but they do not always prove to be satisfying the patient. Although it does not cause death, skin discoloration in vitiligo causes psychological problems and social stigma. Most patients are worried about the worsening of the disease, have disturbed social relationships, feel ashamed, depressed, and have low self-esteem, which in turn can affect the quality of life of vitiligo patients. Thus, vitiligo becomes a problem for patients and health workers who treat them. [1,2,3,4]

The diagnosis of vitiligo is usually made clinically with the aid of a Wood's lamp to determine the extent and activity of the lesion and the response to therapy. Hamzavi et al. introduced a scoring system for vitiligo known as the Vitiligo Area Scoring Index (VASI), which is conceptually analogous to the use of the Psoriasis Area Scoring Index (PASI) score in psoriasis. Vitiligo Area Scoring Index is a semi-quantitative method that has been standardized and sensitive to assess the extent and percentage of depigmentation. This score can also be used to assess the repigmentation that occurs in response to therapy.[1]

Meanwhile, one of the methods for assessing vitiligo disease activity is the Vitiligo Disease Activity Score (VIDA) assessment. This scoring system is a 6-point scale to assess the progression and stability of vitiligo.[5]

The pathophysiological mechanism that causes selective melanocyte apoptosis in vitiligo is not fully understood. Several intrinsic good factors such as autoimmune processes, genetic mutations, impaired migration and proliferation of melanocytes,

stress, imbalance of oxidants and antioxidants (oxidative stress), as well as extrinsic factors such as toxic compounds, phenolic agents, infection, and the presence of trauma are thought to play a role in the occurrence of melanocyte damage in humans. The oxidative stress hypothesis appears to play an important role in the pathogenesis of vitiligo. Some mediators, such as hydrogen peroxide, which occurs in the biosynthesis of melanin, are toxic to the melanocytes themselves, hence the role of antioxidants is needed to eliminate these mediators.[2,6,7]

Zinc is one of the trace elements that have vital functions in the body. Zinc has an antiapoptotic function, neutralizes the toxic effects of antioxidants, and plays a role in melanogenesis.[8,9]

Nooshin et al., concluded from several studies on the role of zinc as an important element in the prevention and treatment of vitiligo based on zinc's functions, namely as an antiapoptotic, as an antioxidant or a buffer against free radicals, as an important element in melanogenesis, stimulating cell-mediated immunity activity to fight infection or other factors that can trigger vitiligo and zinc can stimulate the formation and alpha-melanocyte stimulating hormone.[10]

Because the etiology and pathogenesis of vitiligo are not fully known until now, there has been no established effective and satisfactory treatment for vitiligo; it is deemed necessary to provide a combination of routine therapy with other therapies in order to provide effective and satisfactory results, to improve the patient's quality of life. Until now, research has been done on the role of zinc in vitiligo. Previous studies linking serum zinc levels with the VASI score gave varying results.[4,5,6,7] The study by Zaki et al., concluded a significant negative correlation between serum zinc levels, severity, and vitiligo activity. So it is mentioned that zinc can be a potential supplement in managing vitiligo. Arora et al., in their study, concluded that there was no significant difference in serum zinc levels between vitiligo and non-vitiligo patients.[12,13]

Meanwhile, at the Sanjiwani General Hospital, there has been no research on the correlation of serum zinc levels with the severity of psoriasis. So based on this background, we intend to conduct a study at the Sanjiwani Hospital, Gianyar, which aims to determine the correlation of serum zinc levels with severity as measured by the VASI score and the level of activity of vitiligo as measured by the VIDA score.

METHODS

The research design used in this study was an analytic cross-sectional design aiming to determine the correlation between plasma zinc levels and the severity of

vitiligo using the VASI score and vitiligo disease activity calculated based on the VIDA score.

The study was conducted at Dermatology and Venereology Polyclinic, Sanjiwani Hospital, Gianyar, from June 2021 to December 2021. This study involving 47 subjects of vitiligo patients who met the inclusion and exclusion criteria.

Sampling was carried out using a consecutive sampling technique. This study involved a total of 47 vitiligo patient subjects who met the inclusion and exclusion criteria. Our medical ethic committee approved the study protocol. The study participants have been provided with complete information about the study protocol and have signed the informed consent, and no subjects were lost in this study.

In our research, the dermatologist will collect history, do the physical examination, and asses the severity of the disease (VASI Score) and disease activity (VIDA Score) of the vitiligo subject; then the serum zinc level was examined by taking venous blood. The examination of plasma zinc levels by ELISA method was carried out at the Chemistry Laboratory Analysis of Udayana University.

RESULTS

Characteristics of Research Subjects

The characteristics of vitiligo patients in this study are presented in Table 1.

Table 1. The characteristics of vitiligo patients.

No	Characteristics	Vitiligo (n= 47)	Percentage (%)
1.	Sex		
	Male	19	40.4
	Female	28	59.6
2.	Age (years)		
	≤ 15	5	10.64
	16 – 25	21	44.7
	26 – 35	6	18.4
	36 – 45	6	12.8
	46 – 55	2	4.2
	56 – 65	7	14.9
	≥ 66	0	0
3.	Diagnosis of Vitiligo		
	Non Segmental	29	61.7
	Segmental	18	38.3
4.	Family History		
	Yes	4	8.9
	No	43	91.1
5.	History of injury/trauma in previous vitiligo lesions		
	Yes	12	25.5
	No	35	74.5

This study found 19 patients with vitiligo (40.4%) and 28 women (59.6%). The table above shows that most vitiligo patients are in the age group 16 to 25 years 21 people (44,&%), with a mean age of 31.17 ± 16.01 with a mean onset of disease starting at the age of 26.87 ± 15.63. In the research sample, the non-segmental type of vitiligo was more common than the non-segmental type, 29 (61.7%) compared to 18 (38.3%). The presence of a family history of vitiligo was only found in 4 samples (8.9%). Meanwhile, there were a history of previous trauma or injury in the area of vitiligo lesions found in 12 (25.5%) samples. The average zinc level of vitiligo patients in the sample was 0.203 ± 0.140 nmol/µL.

The severity of vitiligo patients was calculated based on the VASI Score; the average VASI Score was 4.1±3.8. In our study, there were 30 (63.8%) people with mild vitiligo (VASI Score < 5) (63.8%), moderate grade (VASI Score 5-9), as many as 12 people (25.5%), and severe degree (VASI Score > 10) as many as five people (10.6%).

The level of vitiligo disease activity as measured by the VIDA Score was found to be stable in the last one year, and spontaneous repigmentation occurred in 3 people (6.4%), stable in the last year as many as 13 people (27.7%), active in 1 year the last 8 people (17.0%), 10 people were active in the last 6 months (21.3%), 8 people were active in the last 3 months (17.0%), and 5 people were active in the last 6 weeks (10.6%).

Figure 1. Mild Vitiligo

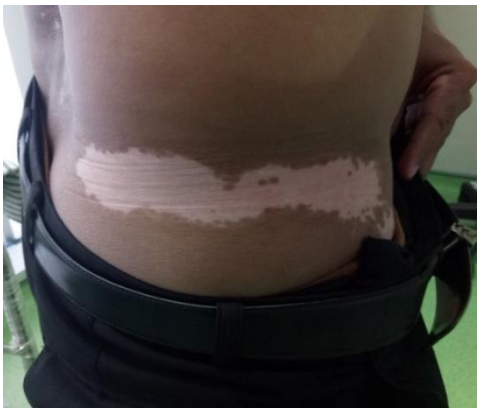

Figure 2. Moderate Vitiligo

Figure 3. Severe Vitiligo

The characteristics of vitiligo patients in our study can be seen on VASI and VIDA Score based in figure 4.

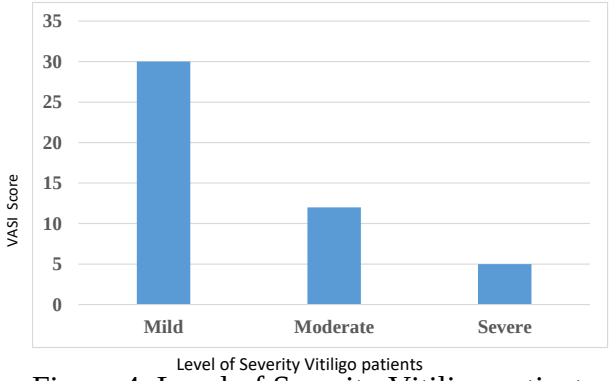

Figure 4. Level of Severity Vitiligo patients based on VASI Score

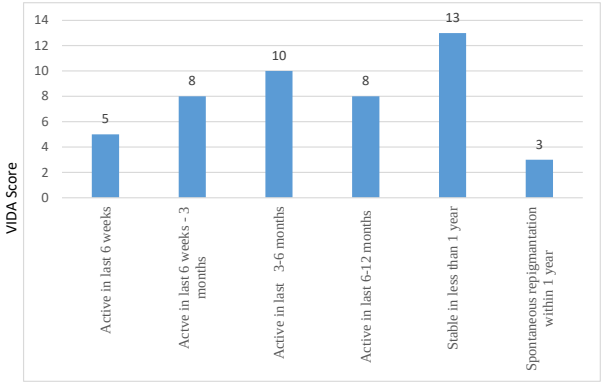

Figure 5. Disease Activity based on VIDA Score

The correlation between vitiligo severity and zinc level and the correlation between vitiligo disease activity and zinc level was analyzed by Spearman's rho statistical test because the data is not normally distributed. This study revealed a strong negative correlation between serum zinc level and the VASI score, with a correlation coefficient r = -0.668 and p <0.05.

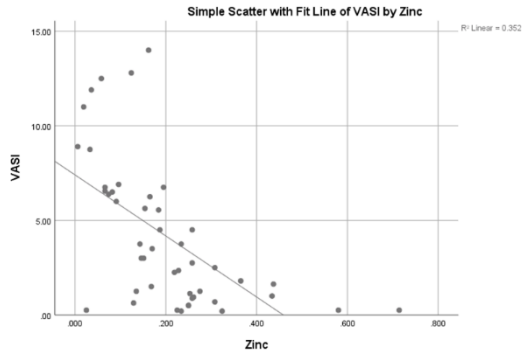

Figure 6. The scattered plot shows that the severity of vitiligo correlated significantly with decreased zinc plasma concentration.

This study found a negative correlation between disease activity and zinc level with r = - 0,342 and p<0,05.

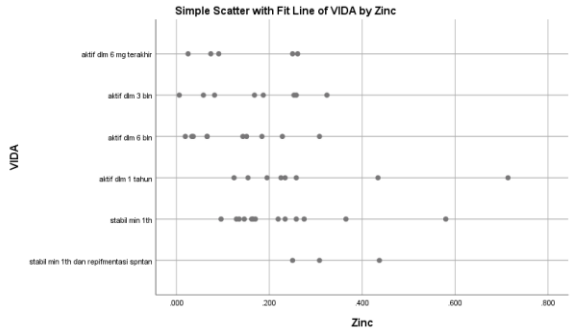

Figure 7. The graphic *scattered plot* shows a negative correlation between the VIDA score and zinc level.

DISCUSSION

Characteristics of Research Subjects

The proportion of vitiligo patients, based on sex, is almost the same. The characteristics of vitiligo patients in our study were more female than male, namely 28 people (59.6%) compared to 19 people (40.4%). The study by Shajil et al. and Daneshpazhooh et al. found a slight trend in women where this may be due to more women coming to seek treatment related to appearance disorders and cosmetic burdens, which is more severe for women. [11,14] Meanwhile, population-based study conducted by Mohr N et al., found a higher prevalence of vitiligo in men than women; in this study, more vitiligo cases were found in the population compared to data from insurance claims showing that there is a significant proportion of vitiligo sufferers who do not come to health services to get therapy.[15]

In this study, vitiligo patients were mostly found in the age group of 16 to 25 years, with an average disease onset starting at 26.87 ± 15.63 years. This is in accordance with several studies showing that all age groups can experience vitiligo, although it usually occurs before the age of 30 years, with almost half of them occurring before the age of 20 years and one-third at the age of 12 years.[16]

There are various classifications of vitiligo diagnosis, one of which is based on the VETF classification; vitiligo is divided into two major groups, namely non-segmental vitiligo and segmental vitiligo. This non-segmental vitiligo includes acrofacial vitiligo, focal vitiligo, mucosal vitiligo, generalized vitiligo, and vitiligo universalis. Vitiligo lesions can occur in any part of the body and generally arise symmetrically or non-segmentally.

Meanwhile, the proportion of segmental vitiligo reaches 10% to 15% of vitiligo patients who come to health services.[16] In this study, the non-segmental type of vitiligo was found to be more common than the non-segmental type, namely 29 (61.7%) compared to 18 (38.3%). Based on family history, 91.1% of vitiligo patients in this study did not have a family history, or only 8.1% had a family history of vitiligo. Galadari et al.'s study, which evaluated 65 people with vitiligo in the United Arab Emirates, found that 19% with a positive family history. In comparison, the study by Onunu and Kubeyinje in Nigeria found a positive family history in 18% of the study population. Although familial clustering is often found in cases of vitiligo, the inheritance seems does not follow the Mendelian pattern. A history of vitiligo in the first-generation family is said to increase the risk of vitiligo by 7-10 times.[10]

Correlation of Serum Zinc Levels with Vitiligo Severity Based on VASI Score and Vitiligo Activity based on VIDA Score

The correlation of serum zinc levels with the severity of vitiligo based on the VASI score with the Spearman's rho correlation test was found a strong negative correlation between serum zinc levels and the VASI score, with the correlation coefficient or r = - 0.609 and p < 0.05, reveals the lower the serum zinc level, the more severe the severity of vitiligo in the sample. This study also found a negative correlation between disease activity and zinc level with r = - 0,342 and p<0,05.

The study conducted by Zaki et al. obtained the same results. There is a strong negative correlation between serum zinc levels and the severity of vitiligo as measured by the VASI Score. In this study, it was also found that the average serum zinc level of vitiligo patients was lower than those of non-vitiligo patients. [13] Narang et al., in their study concluded that zinc and cuprum levels were significantly lower in the vitiligo group but found an insignificant correlation between serum zinc levels and the severity of vitiligo as measured by the VASI Score (Narang et al., 2021). Sriyanifound a weak and insignificant correlation (r = 0.256 ; p = 0.097) between plasma Zn levels and severity after the correlation test was carried out using the Pearson correlation test.

Azzam et al., concluded that there was no significant correlation between serum zinc levels and zinc 2-glycoprotein (ZAG) levels in tissues with VASI and VIDA scores, although the levels of zinc 2-glycoprotein (ZAG) in tissues were significantly lower in patients with vitiligo versus control. Helmy et al., showed that serum zinc and copper levels were significantly higher in active vitiligo

patients compared to controls. While serum zinc and copper levels are insignificantly higher in active vitiligo versus stable disease and in stable patients versus controls. It appears that increased apoptosis of peripheral blood mononuclear cells in active vitiligo will lead to release of zinc and copper in serum (as zinc is present maximally intracellular), resulting in increasing their serum levels significantly in active vitiligo.[18]

Research conducted by Sanad et al. found that the mean serum zinc level decreased significantly in patients with vitiligo and was negatively correlated with levels of inflammatory cytokines such as IL-6, IL-4, and IL-17. In that study, it was concluded that zinc could be useful in treating vitiligo, although the therapeutic dose of zinc requires further research.[17]

Zinc plays an important role in melanogenesis, as tirosinase cofactor and build the intergral part of many metaloenzimes that increase the eumelanin formation.[6] Various physiological, biochemical, histochemical, and enzymatic studies have been done to clarify the pathogenesis of vitiligo.[19] Histological and immunohistochemical studies in prelesional skin suggest the involvement of cellular immunity in vitiligo.[20,21] The auto-cytotoxic theory postulates that cytotoxic precursors to melanin synthesis accumulate in melanocytes, causing cell death (self-destruct theory of Lerner).[22]

Nooshin et al., reveal that zinc is important in preventing and treating vitiligo. The role of zinc in preventing and treating vitiligo with the following mechanisms:

1. Based on histological and some laboratory data, apoptosis of melanocytes has been suggested as a probable mechanism of vitiligo. Zinc, via preventing apoptosis of melanocytes may be able to control vitiligo.
2. One of the theories regarding to pathogenesis of vitiligo is oxidative stress leading to the destruction of melanocytes. Zinc is linked to a cytosolic antioxidant-defense system against reactive oxygen that can inhibit the production of free radicals. Zinc can control vitiligo by inhibiting the production of free radicals.[18,19].
3. Zinc is one of the trace elements that play an important role in the process of melanogenesis.[18,19,25]
4. Some studies, revealed a significant increase in the percentage of apoptotic peripheral blood mononuclear cells invitiligo.[18] On the hand, the accumulation of toxic compounds, altered cellular environment, and infection[24] can all contribute to vitiligo.
5. Zinc may prevent vitiligo by destructing

these probable environmental factors by preventing these immunity-related cells.

6. Zinc may stimulate cell-mediated immunity against probable infective and other factors contributing to vitiligo development.
7. Zinc has a role in the synthesis and release of the α-melanocyte-stimulating hormone in bovine.[25], so that zinc may be effective in melanogenesis in humans by releasing this hormone.
8. Zinc alpha 2 glycoprotein regulates melanin production by normal and malignant melanocytes. They proposed that zinc, via precipitating the ZAG in the site of vitiligo patches, may be effective in treating vitiligo.[14]

Our study reveals a significant negative correlation between serum zinc levels of vitiligo patients and the severity of vitiligo based on the VASI score. This invention could be a sign for further research to determine the main factor that role in the pathogenesis of vitiligo.

CONCLUSION

There is a significant negative correlation between serum zinc levels of vitiligo patients and the severity of vitiligo based on the VASI score. Based on the VIDA score, there is a significant negative correlation between serum zinc levels of vitiligo patients and the degree of vitiligo disease activity.

REFERENCES

1. Alikhan, A., Felsten L.M., Daly, M., Petronic-Rosic, V. 2011. Vitiligo: A Comprehensive Overview. J Am Acad Dermatol; 65(3): 473-91.
2. Birlea, S.A., Spritz, R.A., Norris, D.A. 2012. Vitiligo In: Wolff, K., Goldsmith, L.A., Katz, S.I., Gilchrest, B.A., Paller, A.S., Leffell, D.J., Eds. Fitzpatrick's Dermatology In General Medicine. 8th Ed. New York: McGraw Hill. p.792-803.
3. Ingordo, V., Lannazzone, S, et al. Dermatology Life Quality Index Score in Vitiligo Patients: A Pilot Study Among Young Italian Males. G Ital Dermatol Venereol. 2011; 146:1-2
4. Hedayat, K.,Karbashsh, et al. Quality of Life in Patient with Vitilgo: A Cross-Sectional Study Based in Vitiligo Quality of Life Index (VitiQol). Health and Quality of Life Outcomes. 2016; 14: 86
5. Alghamdi, K.M., Kumar, A., Taieb, A., Ezzedine, K. 2012. Assessment Methods for The Evaluation of Vitiligo. JEADV; 26: 1463-71.

6. Bagherani, N., Yaghoobi, R., Omidian, M. Hypothesis: Zinc can be effective in treatment of vitiligo. Indian J Dermatol. 2011;56:480-4.
7. Mohammed, GF., Gomaa, AH. Al-Dhubaibi, MS. Highlights in pathogenesis of vitiligo. World J Clin Cases. 2015;3:221-30
8. Cohen, B., Elbuluk., et al. Alternatif systemic treatments for vitiligo: A review. Am J Clin Dermatol. 2015;16: 463-74.
9. Zeng Q, et al. Decreased copper and zinc in sera of Chinese vitiligo patients: A meta-analysis. J Dermatol. 2014;41:245-51
10. Bagherani, N., Yaghoobi, R., Omidian, M. Hypothesis: Zinc can be effective in treatment of vitiligo. Indian J Dermatol. 2011; 56 (5):480-84.
11. Daneshpazhooh M, Mostofizadeh G, Behjati J, Akhyani M, Robati MR. Anti-thyroid peroxidase antibody and vitiligo: A controlled study. BMC Dermatol. 2006;6:3
12. Arora, PN., et al. Serum zinc level in cutaneus disorder. Med J Armed Force India. 2002; 58:304-6.
13. Zaki, M., Nada, A., Elshahed, A. Therapeutic of assessment of serum zinc level in patients with vitiligo: A patient controlled prospective study. Dermatology therapy. 2020; 33 (3):1-4.
14. Yanghoobi R, Omidian M, Bagherani N. Vitiligo: A review of the published work 2011:38:419-31. J Dermatol. 2011:38:419-31.
15. Mohr N, Petersen J, Kirsten N, Augustin M. Epidemiology of Vitiligo - A Dual Population-Based Approach. Clin Epidemiol. 2021 May 26;13:373-382.
16. Ezzedine, Khaled & Eleftheriadou, Viktoria & Whitton, Maxine & Geel, Nanja. (2015). Vitiligo. Lancet. 386. 10.
17. Sanad EM, El-Fallah AA, Al-Doori AR, Salem RM. Serum Zinc and Inflammatory Cytokines in Vitiligo. J Clin Aesthet Dermatol. 2020 Dec;13(12 Suppl 1):S29-S33. Epub 2020 Dec 1.
18. Helmy MI, Gayyar EL, Hawas S, Eissa AE. Role of oxidative stress in the pathogenesis of vitiligo. J Pan-Arab League Dermatologist. 2004;15:97–105.
19. Shameer P, Prasad PV, Kaviarasan PK. Serum zinc level in vitiligo: A case-control study. Indian J Dermatol Veneol Leprol. 2005;71:206–7.
20. Pichler R, Sfetsos K, Badics B, Gutenbrunner S, Berg J, Auböck J. Lymphocyte imbalance in vitiligo

patients indicated by elevated CD4+/CD8+ T-cell ratio. Wien Med Wochenschr. 2009;159:337–41.

21. Ongenae K, Van Geel N, Naeyeert JM. Evidence for an autoimmune pathogenesis of vitiligo. Pigment Cell Res. 2003;16:90–100.
22. Burns T, Breathnach S, Cox N, Griffiths C. 7th ed. Vol. 2. Oxford: Blackwell Science; 2004. Rook's Textbook of Dermatology; pp. 53– 7.
23. Inamadar AC, Palit A. Acrodermatitis entropathica with depigmented skin lesions simulating vitiligo. Pediatr Dermatol. 2007;24:668– 9.
24. Boisy RE, Spritz RA. Frontiers and controversies in the pathobiology of vitiligo: Separating the wheat from chaff. Exp Dermatol. 2009;18:583–5.
25. Inamadar AC, Palit A. Acrodermatitis entropathica with depigmented skin lesions simulating vitiligo. Pediatr Dermatol. 2007;24:668–9