The Relationship between Serum Zinc Level and Severity of Melasma

Puspita Sari Rambe*, Rointan Simanungkalit, Ariyati Yosi****

*Post graduate of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
**Departement of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

DOI: 10.29322/IJSRP.10.01.2020.p9749
http://dx.doi.org/10.29322/IJSRP.10.01.2020.p9749

***Abstract*- Introduction:** Melasma is an acquired, chronic, hyperpigmentation disorder which characterized by light-brown to bluish-gray macules and patches. Some researchers have reported an association between low serum zinc levels and various dermatological conditions including melasma. Zinc is one of the essential micronutrients known to play a role in the etiopathogenesis of melasma through its anti-inflammatory and antioxidant effects. To date, no research has been conducted to assess the relationship of serum zinc levels with the severity of melasma.

Objective: To evaluate the relationship between serum zinc levels and disease severity in melasma patients

Methods: This is an observational analytic studies using cross sectional design to assess the relationship between serum zinc levels and the severity of melasma in 30 melasma patients. MASI score calculation is done to assess the severity of melasma. Serum zinc levels was measured by Agilent 7700 Series Inductively Coupled Plasma - Mass Spectrophotometry (ICP-MS).

Results: The average serum zinc level in melasma patients with mild, moderate and severe melasma were 54.31 µg/dL, 53.56 µg/dL and 47 µg/dL respectively. Most of the melasma patients were in the age group 36-45 years (43.3%), with occupation as a laborer/farmer (56.7%) and the main predisposing factor due to sun exposure (36.7%). Centrofacial and malar patterns were seen in 80% and 20% of patients, respectively, and no mandibular patterns were found. Most types of melasma are epidermal types (80%), followed by dermal types (20%) and no mixed types were found.

Conclusion: There was no significant relationship between serum zinc levels and the severity of melasma. This is the first study to assess the relationship between serum zinc levels with the severity of melasma, and can be a reference to conduct similar research with good methodological design.

***Index Terms*-** melasma, zinc, serum level, MASI score

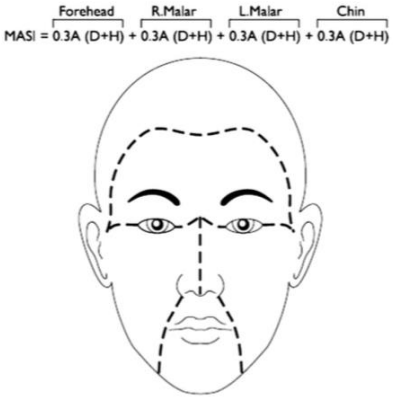
I. Introduction

Melasma is an acquired, chronic, hyperpigmentation disorder which characterized by light-brown to bluish-gray macules and patches. Melasma usually affects the chronically sun exposed area, especially the face and neck.[1] Melasma is most often found in women and in darker skin types. The prevalence of melasma was reported to range from 8.8% among Latin women in the Southern United States to as high as 40% in Southeast Asia.[2] In Indonesia, the ratio of cases of women and men was 24:1, with the highest incidence was in women aged 30-44 years. Cases of melasma are especially seen in women of childbearing age with a history of direct sun exposure.[3]

Clinical features of melasma include brown to grayish patches on sun-exposed areas of the face. Three clinical patterns of distribution of melasma are described: centrofacial, malar and mandibular.[1] Based on the location of pigment deposits, melasma is divided into 3 types: epidermal, dermal, and mixed types. The epidermal type is most often encountered and characterized by light brown hyperpigmentation, Wood's light enhances the color contrast between hyperpigmented areas and normal skin. Dermal type melasma is characterized by bluish-gray hyperpigmentation and exhibits no accentuation of color contrast under wood's light. Mixed type melasma is characterized by dark brown hyperpigmentation, and Wood's light enhances the color contrast in some areas, whereas others show no change.[4]

The severity of melasma can be measured by calculating the MASI score. The MASI score was first developed by Kimbrough-Green, et al in 1994 to assess the severity of melasma clinically. The MASI scores is calculated by subjective assessment of 3 factors: the area involved (area/A), darkness (D), and homogeneity (H), with the forehead (f),right malar region (rm), left malar region, (lm), and chin (c) corresponding to 30%, 30%, 30% and 10% of the total face, respectively (Fig 1).[5]

Fig 1. *Melasma Area Severity Index* (MASI)



The etiopathogenesis of melasma is still not fully understood. Various internal and environmental factors play a role in melasma, including genetic predisposing factors, sun exposure and hormonal factors.[1,2] Sun exposure is one of the important

factors causing melasma. The acute effect of exposure to Ultra Violet (UV) light on human skin involves several mechanisms such as a direct effect on keratinocytes to release melanogenic and inflammatory factors on fibroblasts that stimulate melanogenesis.[6] Exposure to UV light can also result in the formation of Reactive Oxygen Species (ROS), causes damages lipids, proteins and deoxyribonucleic acid (DNA), thus forming pyrimidine photoproducts, causing lipid peroxidase which ultimately produces nitric oxide (NO), as well as cytokines and enzymes that play a role in the inflammatory process.[7] Furthermore, inflammatory cytokines and free radicals will increase proliferation melanocytes and increase melanin synthesis through tyrosinase activity.[1]

Zinc is an essential trace elements for humans. It is an essential component of more than 300 metalloenzymes and over 2000 transcription factors that are needed for regulation of lipid, protein and nucleic acid metabolism, and gene transcription. Some researchers have reported an association between low serum zinc level and various dermatological conditions including melasma, acne vulgaris, rosacea, vitiligo, leprosy, verruca vulgaris, alopecia areata, and hidradenitis suppurativa.[8] Zinc can be used as an effective agent for the treatment of several dermatological disorders, especially those that are associated with zinc deficiency, but there is little evidence to support the effectiveness of zinc as a first-line therapy in most dermatological conditions.[9]

Zinc influences the immune response and shows anti-inflammatory and antioxidant activity.[10] Several studies conducted in humans indicate that zinc has a protective effect against free radical formation and oxidative stress.[11] Zinc is anti-inflammatory by inhibiting the production of cytokines and inflammatory mediators.[1]

Research that reports the effectiveness of topical zinc therapy in melasma patients has been conducted although it is still limited. Sharquie *et al*, was evaluated the efficacy of 10% zinc sulphate solution in 14 patients and found a percentage improvement in Melasma Area Severity Index (MASI) score by 49.7% which was statistically significant.[12] Another study was conducted by Iraji *et al* which comparing the effectiveness of 10% zinc sulphate solution with 4% hydroquinone. Of 72 melasma patients, there was a reduction in MASI scores in both groups after two months, but a more significant reduction was found in the group receiving hydroquinone.[13] Similar results were obtained in a study conducted by Yousefi *et al* comparing 10% zinc sulphate with hydroquinone 4 %. Of the 82 melasma patients, a significant reduction in MASI score was obtained from both groups, but a greater decrease was found in those who received hydroquinone.[14] Research by Younas *et al* in 70 melasma patients treated with 10% zinc sulphate found a reduction in MASI score of 47.36%, and concluded that zinc sulphate was a cheap, safe and effective agent for the treatment of melasma.[15]

Research on serum zinc levels in melasma patients conducted by Rostami *et al* states that there is a significant relationship between low zinc levels and melasma.[16] To date, no research has been conducted to assess the relationship of serum zinc levels with the severity of melasma.

II. METHODS

This was an observational analytic study using a cross sectional design which was conducted from April to December 2019. Patients presenting with melasma to the dermatology outpatient clinic of H. Adam Malik General Hospital Medan were recruited as the study subjects. The inclusion criteria for patients with melasma were as follow: being over 25 years of age and signed informed consent before entering the study. Exclusion criteria were pregnant and breastfeeding patients and under treatment with zinc within 1 month before the study. This study was approved by the Research Ethics Commission of the Faculty of Medicine, Universitas Sumatera Utara / H. Adam Malik General Hospital Medan.

III. RESULTS

A total of 30 female melasma patients were enrolled in this study. Patients were characterized by age, occupation, predisposing factors, melasma pattern and type of melasma (Table 1). Most common age was 36-45 years (43.3%), followed by 46-55 (36.7%). Regarding occupation, majority of the study subjects were laborers/farmers (56.7%), followed by professional (20.0%), and housewife (13.3%). The most predisposing factors due to sun exposure (36.7%), followed by a combined factor of sun exposure and contraception (23.3%) and unknown predisposing factors (20 %). Regarding the patterns of melasma, centrofacial pattern was the most common seen in 24 (80%) patients. The next common pattern seen was malar observed in 6 (20%) patients. Mandibular pattern was not found in this study. On Wood's lamp examination, epidermal type of pigmentation was the commonest type seen in 27 (90%) patients, followed by dermal type seen in 3 (10%) patients and no mixed types were found.

Table 1. Patient characteristics

Characteristics	Subject	
	Frequency (n)	Percentage (%)
Age (years)		
26-35	2	6.7
36-45	13	43.3
46-55	11	36.7
56-65	4	13.3
Occupation		
Housewife	4	13.3
Laborer/farmer	17	56.7
Professional	6	20
Bussiness	3	10
Predisposing factor		
None	6	20
Sun exposure	11	36.7
Contraception	3	10
Pregnancy	2	6.7
Sun exposure and contraception	7	23.3
Sun exposure and pregnancy	1	3.3
Melasma pattern		
Centrofacial	24	80
Malar	6	20
Mandibular	0	0
Melasma type		
Epidemal	27	90
Dermal	3	10
Mix	0	0

Based on our study, the mean duration of the melasma was 91.70±72.145months with a minimum value of 12 months and a maximum value of 240 months. The relationship of serum zinc levels with melasma duration were presented in Table 2. Based on our study, the result of Spearman correlation test showed the value of $p > 0.05$. There is no significant relationship between serum zinc levels with duration of melasma (p-value = 0.680, r = 0.079).

Table 2 Relationship of serum zinc levels with duration of melasma

	min-max (months)	**Mean ± SD (months)**	**r**	***p*-value**
Duration of melasma	12-240	91.70 ± 72.145	0.079	0.680

From the MASI score, the severity of melasma was mild in 13 patients, moderate in 16 patients and severe in 1 patient. Serum zinc levels in mild melasma patients ranged from 42-70 µg/dL (mean 54.31 µg/dL), moderate 34-72 µg/dL (mean 53.56 µg/dL), and severe 47 µg/dL (Table 3).

Table 3. Relationship of serum zinc levels with the severity of melasma

Melasma severity	**n**	**Min-Max (µg/dL)**	**Mean ± SD (µg/dL)**	***p*-value**
Mild	13	42-70	54.31 ± 7.307	
Moderate	16	34-72	53.56 ± 8.951	0.542
Severe	1	47-47	47	

Based on our study, the results of the kruskal-wallis test showed the value of $p > 0.05$. There is no significant relationship between serum zinc levels with the severity of melasma ($p > 0.05$).

IV. DISCUSSIONS

In our study, the highest number of melasma subjects was 36-45 years (43.3%) and followed by 46-55 years (36.7%). A similar study by Umborowati *et al* reported the majority of melasma patients was 36-45 year (43%), followed by the 46-55 year.[17] In our study, most subjects had working outdoors and often exposed to sunlight, especially in the laborers/farmers groups. Research conducted by Handel *et al* revealed a higher proportion of individual melasma who reported work with higher sun exposure. Chronic sun exposure is more important in developing melasma.[18]

The most predisposing factors found in this study were due to sun exposure as many as 11 cases (36.7%) and the second most were combined factors of sun exposure and contraception as many as 7 cases (23.3%). Sun exposure is one of the important factors causing melasma with the formation of ROS which causes lipid peroxidation and produces free radicals and the release of inflammatory cytokines thereby increasing the process of melanogenesis.[1] Hormonal factors are also referred to as important factors triggering the occurrence of melasma. Estrogen, progesterone and MSH may induce hyperpigmentary responses within melanocytes by increases tyrosinase and dopachrome tautomerase resulting in the process of melanogenesis.[19]

Melasma involving sun exposed areas, such as face and less commonly on neck and arms. During exposure and after sun exposure, clinical manifestations are more clearly visible. Centrofacial melasma are more common because the appropriate area of focus is direct sun exposure. In our study, the most frequent pattern of melasma was the centrofacial pattern of 24 patients (80%), followed by the malar pattern of 6 patients (20%). Mandibular pattern was not found in this study. This result is similar with study by Kusumaningrum *et al*. Centrofacial pattern was the most common pattern (87.5%), followed by malar pattern (12.5%) and no subjects with mandibular type were found.[20] The type of melasma is determined based on clinical examination and Wood's lamp. The epidermal type was found more frequently in (90%), followed by dermal types (10%) and no mixed types were found.

Based on table 2 it can be seen that there is no significant relationship between serum zinc levels with melasma duration (*p*-

value = 0.680, r = 0.079). This study is similar with research conducted by Rostami et al who stated that there was no significant relationship between serum zinc levels and duration of melasma (*p*-value = 0.182).[16]

Based on table 3 it can be seen that there is no significant relationship between serum zinc levels with the severity of melasma ($p > 0.05$). The previous study conducted by Rostami *et al* found that there was a relationship between low zinc levels in melasma patients. Serum zinc levels in control subjects ranged from 45.3 – 130.4 µg/dL with a mean value of 82.2 ± 23.9 µg/dL, while serum zinc levels in melasma patients ranged from 39.1 – 126.5 µg/dL with a mean value of 77.4 ± 23.2 µg/dL. Paired t test results showed that there were significant differences between serum zinc levels in melasma patients compared with control subjects (P-value 0.0001). Serum zinc deficiency was found in 54 (45.8%) in melasma patients and 28 (23.7%) in control subjects.[16] Low zinc levels were also encountered in our study, where 24 subjects (80%) had serum zinc levels below normal (<60 µg/dL). Etiopathogenesis of melasma is complex in which sun exposure is one of the main causative factors. UV light can cause the formation of ROS which in turn will cause lipid peroxidation and stimulate the release of inflammatory cytokines and subsequently stimulate the process of melanogenesis.[1,7] Zinc in this case is a SOD enzyme cofactor which is one of the main antioxidants in fighting ROS.[10,21]

There is no significant relationship between serum zinc levels and the severity of melasma in this study, indicating that melasma is not only influenced by sun exposure, but is multifactorial, such as genetic, hormonal, and other factors (drugs, neural and psychological and lipid metabolism).

V. CONCLUSIONS

This study shows that there is no significant relationship between serum zinc levels and the severity of melasma. This is the first study to evaluate the relationship of serum zinc levels and the severity of melasma so that it can be used as a reference to conduct similar studies in the future with a better design methodology.

REFERENCES

[1] Bagherani N, Gianfaldoni S, Smoller B. An overview on melasma. Pigmentary disorders. [Internet]. 2015 [cited 2019 Juni 21]; 2(10): 1-8. Available from https://www.omicsonline.org/open-access/an-overview-on-melasma-2376-0427-1000216.php?aid=60663
doi:10.4172/2376-0427.1000216

[2] Park KC, Kang HY. Current Views on Melasma. In: Kumarasinghe P. (eds) Pigmentary Skin Disorders. Updates in Clinical Dermatology. Springer, Cham. [Internet]. 2018 [cited 2019 Juni 21]. Available from:
https://link.springer.com/chapter/10.1007/978-3-319-70419-7_12

[3] Soepardiman L. Kelainan pigmen. Dalam: Djuanda A, Hamzah, Aisah S, editor. Ilmu Penyakit Kulit dan Kelamin Edisi ke 7. Jakarta: Balai Penerbit FKUI. 2015; 342-345.

[4] Rigopoulos D, Gregoriou S, Katsambas A. Hyperpigmentation and melasma. Journal of Cosmetic Dermatology. [Internet]. 2007 [cited 2019 Juni 22]; 6(3): 195–202. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1473-2165.2007.00321.x
doi:10.1111/j.1473-2165.2007.00321.x

[5] Pandya AG, Hynan LS, Bhore R. Reliability assessment and validation of the Melasma Area and Severity Index (MASI) and a new modified MASI scoring method. Journal of American Academy of Dermatology. [Internet]. 2009 [cited 2019 Juni 22]; 6(1):78-83.e2. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20398960
doi10.1016/j.jaad.2009.10.051

[6] Lee AY. Recent progress in melasma pathogenesis. Pigment cell & melanoma research. [Internet]. 2015 [cited 2019 Juni 22]; 28(6): 648-60. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/pcmr.1240

[7] Nishisgori C. Current concept of photocarcinogenesis. Photochemical & Photobiological Sciences. [Internet]. 2015 [cited 2019 Juni 22]; 14(9): 1713-21. Available from: https://pubs.rsc.org/en/content/articlehtml/2015/pp/c5pp00185

[8] Mrinal Gupta, Vikram K. Mahajan. Zinc Therapy in Dermatology: A Review. Dermatology Research and Practice. [Internet]. 2014 [cited 2019 Juni 21], Article ID 709152, 11 pages. Available from: https://www.hindawi.com/journals/drp/2014/709152/cta/
doi 10.1155/2014/709152

[9] Bagherani N, Smoller B. An overview of zinc and its importance in dermatology-Part II: The association of zinc with some dermatologic disorders. Global dermatology. [Internet]. 2016 [cited 2019 Juni 21]; 3(5): 337-50. Available from: https://www.oatext.com/pdf/GOD-3-186.pdf
doi: 10.15761/GOD.1000186

[10] Jarosz M, Olbert M, Wyszogrodzka G. Antioxidant and anti-inflammatory effects of zinc. Zinc-dependent NF-κB signaling. Inflammopharmacology. [Internet]. 2017 [cited 2019 Juni 26]; 25(1): 11–24. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5306179/
doi:10.1007/s10787-017-0309-4

[11] Rostan EF, Debuy HV. Evidence supporting zinc as an important antioxidant for skin. International Journal of Dermatology. [Internet]. 2001[cited Juni 26]; 41: 606-611. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12358835
doi:10.1046/j.1365-4362.2002.01567.x

[12] Sharquie KE, Al Mashhadani SA. Topical 10% zinc sulfate solution for treatment of melasma. Dermatology surgery. [Internet]. 2008 [cited 2019 Juni 22]; 34: 10. Available from:
https://www.ncbi.nlm.nih.gov/pubmed/18616534
DOI:10.1111/j.1524-4725.2008.34287.x

[13] Iraji F, Tagmirriahi N, Gavidnia K. Comparison between the efficacy of 10% zinc sulfate solution with 4% hydroquinone cream on improvement of melasma. Adv Biomed Res. [Internet]. 2012 [cited 2019 Juni 22]; 1(3): 39. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3544106/
doi:10.4103/2277-9175.10013

[14] Yousefi A, Khoozani Z. Is topical zinc effective in the treatment of melasma? A double-Blind randomized comparative study. Dermatol surgery. [Internet]. 2014 [cited 2019 Juni 21]; 40(1): 33-7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24237751
doi: 10.1111/dsu.122

[15] Younas S, Fasih S, Arshad A. Outcome of topical 10% zinc sulphate solution in the treatment of melasma. Pak J Physiol [Internet]. 2019 [cited 2019 November 22]; 15(1): 45-47. Available from: http://www.pps.org.pk/PJP/15-1/Sana.pdf

[16] Rostami M, Ardabili N. Evaluation of the serum zinc level in adult patients with melasma: Is there a relationship with serum zinc deficiency and melasma? J Cosmet Dermatol. [Internet]. 2018 [cited 2019 April]; 17(3): 417-422. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29131489
doi: 10.1111/jocd.12392

[17] Umborowati MA, Rahmadewi. Studi Retrospektif: Diagnosis dan Terapi Pasien Melasma. BIKKK - Berkala Ilmu Kesehatan Kulit dan Kelamin - Periodical of Dermatology and Venereology. 2014; 26(1): 56-62.

[18] Handel AC, Lima PB, Tonolli V. Risk factors for facial melasma in women: a case-control study. British Journal of Dermatology. [Internet]. 2014 [cited 2019 October 5]; 171(3): 588–594. Available from: https://onlinelibrary.wiley.com/doi/pdf/10.1111/bjd.13059
doi:10.1111/bjd.13059

[19] Costin GE, Birlea SA. What is the mechanism for melasma that so commonly accompanies human pregnancy. Life. [Internet]. 2006 [cited 2019 Juli 16]; 58 (1): 55-7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/16540433
doi10.1080/15216540500417020

[20] Kusumaningrum N, Febriana SA, Winarni DR. Fungsi Barier Kulit pada Pasien Melasma. Media Dermato Venereologica Indonesiana. [Internet].

2018 [cited 2019 October 16]; 45(3). Available from: http://www.ojs.perdoski.id/index.php/mdvi/article/view/3
doi 10.33820/mdvi.v45i3.3

[21] Seckin HY, Kalkan G, Bas Y. Oxidative stress status in patients with melasma, Cutan ocul toxicol. [Internet]. 2014 [cited 2019 October 16]; 33(3): 212-217. Available from:
https://www.ncbi.nlm.nih.gov/pubmed/24147944
doi:10.3109/15569527.2013.834496

AUTHORS

First Author – Puspita Sari Rambe, Post graduate of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia, Email: pipitrambe@gmail.com
Second Author – Rointan Simanungkalit, Departement of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia
Third Author – Ariyati Yosi, Departement of Dermatology and Venereology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia