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Original Article

Low plasma melatonin levels negatively-correlate with melasma severity

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Abstract

Background: Chronic exposure to ultraviolet light plays a role in the pathogenesis of melasma. Exposure to excessive sunlight leads to the formation of free radicals. As a result, the body responds by forming antioxidants such as melatonin, which is activated through the melatoninergic antioxidative system to fight oxidative stress. The relationship between melatonin and melasma is yet to be elucidated. This study aims to determine the correlation between melatonin and the severity of melasma.
Methods: This analytical cross-sectional study involved 50 melasma subjects and 10 non-melasma subjects who met the inclusion criteria and were aged between 21-50 years at Prof. I.G.N.G. Ngoerah National General Hospital, Denpasar. The severity of melasma was measured by calculating the melasma area severity index (MASI) score and plasma melatonin levels were assessed using the ELISA method.
Results: The median plasma melatonin level in the melasma subjects was lower (92.48 ng/ml) than in non-melasma subjects (436.35 ng/ml), with a p-value of <0.001. Low plasma melatonin levels strongly- and negatively-correlated with melasma severity (r=-0.707; p<0.001), with a prevalence ratio (PR) of 2.875 [95% confidence interval (CI) = 1.605-5.150, p<0.001].
Conclusion: Low plasma melatonin levels negatively-correlate with the severity of melasma.

Keywords: *melasma, melatonin, melasma severity index*

Background

Melasma is a common hyperpigmentation disorder characterized by irregular brown to dark brown patches on the facial areas exposed to sunlight. Melasma can affect all ethnicities, but it is more common in individuals with Fitzpatrick skin types IV and V. This pigmentation disorder often causes great emotional burden due to disturbance in facial appearance.[1,2] Melasma has a complex and mostly unknown pathogenesis, often leading to treatment failure and high recurrence.[1,3] The etiopathogenesis of melasma is influenced by factors such as sun exposure, genetic predisposition, hormones, drugs, thyroid disease, oxidative stress, and the role of dermis and vascular components.[4-6] Solar radiation can induce alpha-melanocyte-stimulating hormone (α-MSH), corticotropin, and lipid peroxidase, causing increased production of melanin by melanocytes.[4] Ultraviolet (UV) radiation and visible light cause the formation of lipid peroxidase in the cell membrane, resulting in the formation of free radicals, which can induce melanogenesis. Continuous exposure to ultraviolet radiation can lead to a decrease in skin antioxidant capacity, causing oxidative damage and stimulating skin hyperpigmentation.[5]

To prevent oxidative stress, skin organs produce protective molecules, including melatonin – a derivative of serotonin, which has a decreased capacity due to the aging process and oxidative damage. Melatonin is a neuroendocrine secreted by the pineal gland, which regulates the circadian rhythm and skin redox status and promotes sleep.[7-9] Melatonin can also be found in the skin, which

provides a protective effect against skin damage due to external factors. Other functions include limiting oxidative stress, stimulating the production of antioxidant enzymes, repairing DNA damage, and providing anti-inflammatory and anti-apoptotic effects.[6,10] The role of melatonin in regulating skin pigmentation and its intracutaneous synthesis is not yet apparent.[10,11] Moreover, the association between melatonin and the pathogenesis of melasma has not been widely studied. This study aims to determine the correlation between melatonin and melasma.

Methods

This analytical observational study used a cross-sectional design. It involved 50 melasma subjects and 10 non-melasma subjects who met the inclusion criteria with an age range of 21-50 years at the Dermatology and Venereology Clinic of Prof. I.G.N.G. Ngoerah National General Hospital, Denpasar. The exclusion criteria are patients with melasma with chronic systemic diseases, internal organ malignancies, pregnancy, menopause, obesity, and immunocompromised conditions, as well as patients currently undergoing hormone replacement therapy, using hormonal contraception, and subjects who have consumed melatonin systemically or topically in the past four weeks. Ten individuals who were relatives of patients were assigned as controls. These age-matched controls did not have melasma or any other skin condition.

The patient's histories were taken, and then physical examination and calculation of the severity of melasma using the melasma area severity index (MASI) score were performed. The cut-off point of the MASI score was based on the mean value. Examination of plasma melatonin levels was conducted at the Clinical Pathology Laboratory of Prof. I.G.N.G. Ngoerah National General Hospital, Denpasar. Wood's lamp examination is used to determine the depth of melasma lesions. Epidermal lesions will appear clearer when exposed to Wood's lamp, while dermal lesions will appear increasingly unclear. The mixed type represents a combination of both presentations.

Plasma sample was obtained from 3 ml venous blood of each subject collected at 8–9 a.m. Melatonin levels were examined using the enzyme-linked immunosorbent assay (ELISA) method. The examination results were presented as numerical data in units of ng/L. The data obtained were analyzed using univariate analysis to calculate frequencies and percentages. Comparative analysis using the Mann-Whitney test was performed to determine the difference in median melatonin levels between melasma and non-melasma subjects. A cut-off point was determined based on the median value to categorize the results of melatonin levels from ELISA examinations into low and high.

Spearman's Rho test was performed to assess the correlation between plasma melatonin levels and the severity of melasma. Prevalence ratio (PR) was used to compare conditions between the two different groups using the Chi-square test. Statistical package for social sciences (SPSS) software version 22 (IBM Corp, New York, United States) was used for data analysis. This study has received approval from the Medical Research Ethics Commission (KEPK) of the Faculty of Medicine, Udayana University under ethical clearance number 2019.02.1.1440.

Results

This study involved 60 subjects consisting of 50 melasma subjects and 10 non-melasma subjects. The melasma subjects consisted of 18 males (36%) and 32 females (64%). Table 1 presents the characteristics of melasma subjects including sex, age, skin type, ultraviolet exposure duration, melasma pattern, and melasma severity levels. The largest age group for melasma subjects was 31-40 years. The lowest age was 25, and the highest was 50. The control group had 2 (20%) subject aged 21-30 years and 8 (80%) aged 31-40 years. Twenty-seven patients (54%) in the melasma group had Fitzpatrick skin type IV and 23 (46%) had Fitzpatrick skin type V. Six subjects (60%) in the control group had Fitzpatrick skin type IV and 4 (40%) had Fitzpatrick skin type V.

The study found that 50 subjects (100%) with melasma worked outdoors as security guards, salesmen, parking attendants, traffic police, and ticket takers who in their daily activities were exposed to sunlight. They have an average exposure to sunlight of more than 2 hours per day. The most common pattern of melasma was the centrofacial pattern found in 37 subjects (74%), followed by the malar pattern in 11 subjects (22%), and the mandibular pattern in 2 subjects (4%). Wood's lamp examination revealed that among 50 patients with melasma, 37 (74%) had mixed type pattern, 10 (20%) showed an epidermal type pattern, and the least common was the dermal type pattern observed in 3 patients (6%).

Melasma severity levels were calculated based on the MASI score of 50 melasma subjects. The

results of the study showed a mild degree in 11 subjects (22%), a moderate degree in 31 subjects (62%), and a severe degree in 8 subjects (6%). This study also found statistically significant differences in plasma melatonin levels between melasma and non-melasma subjects (p<0.001), as seen in Table 2. Our results showed a strong and statistically significant negative correlation between plasma melatonin levels and the severity of melasma in melasma subjects (r=-0.707; p<0.001), as shown in Table 3.

Table 1. Characteristics of Subjects

Variables	Group		p-value
	Melasma n=50 (%)	Non-Melasma n=10 (%)	
Sex			
Female	32 (64%)	5 (50%)	0.8
Male	18 (36%)	5 (50%)	
Age			
21-30 years	13 (26%)	2 (20%)	0.5
31-40 years	27 (54%)	8 (80%)	
41-50 years	10 (20%)	-	
Fitzpatrick Skin Type			
Fitzpatrick IV	27 (54%)	6 (60%)	0.04*
Fitzpatrick V	23 (46%)	4 (40%)	
Ultraviolet exposure duration			
>2 hours	50 (100%)	-	0.032*
≤2 hours	-	10 (100%)	
Melasma pattern			
Centrofacial	37 (74%)	none†	none
Malar	11 (22%)	none	none
Mandibular	2 (4%)	none	none
Melasma type			
Epidermal	10 (20%)	none	none
Dermal	3 (6%)	none	none
Mixed	37 (74%)	none	none
Melasma severity level			
Mild	11 (22%)	none	none
Moderate	31 (62%)	none	none
Severe	8 (6%)	none	none

*Significance at p<0.05; †: not evaluated in non-melasma subjects

Table 2. Comparison of Plasma Melatonin Levels between Melasma and Non-Melasma Subjects

Variable	Group		p-value
	Melasma (n=50)	Non-melasma (n=10)	
Melatonin (ng/L)	92.480	436.355	<0.001*[a]
Median (minimum-maximum) (ng/L)	92.48 (32.41 - 302.78)	436.36 (421.14 - 447.37)	

*Significance at p<0.05; [a]: Mann-Whitney test

Table 3. Correlation between Plasma Melatonin Level and Melasma Severity in Melasma Subjects

Variable (n=50)	Melasma Severity Level	
	r	p value
Plasma melatonin level	-0.707	<0.001*

*Significance at p<0.05; r: Spearman correlation coefficient

Table 4. Comparison of Melasma Occurrences by Plasma Melatonin Level Categories in Melasma Subjects

Melatonin Level	Melasma Group		PR	95% CI	p value
	Mild Melasma (<19.45)	Severe Melasma (≥19.45)			
Low (<92.48 ng/L)	2 (8%)	23 (92%)	2.87	1.605-5.150	<0.001*
High (≥92.48 ng/L)	17 (68%)	8 (32%)			

*Significance at p<0.05; CI: confidence interval; PR: prevalence ratio

Table 4 presents a comparison of melasma occurrences by plasma melatonin level categories. Low plasma melatonin levels increase the PR of melasma. Low plasma melatonin levels can increase the risk of melasma by 2.87 times (PR 2.87; 95% CI = 1.605-5.150; p<0.001) compared to high plasma melatonin levels.

Discussion

The pathogenesis of melasma is highly complex, involving various pathways in the induction of hyperpigmentation. Overexposure to sunlight is one of the etiologic factors for melasma.[12,13] UV exposure on the skin produces reactive oxygen species (ROS), resulting in oxidative stress when the body's antioxidant defenses are overwhelmed.[14] Current research has proven the role of oxidative stress in the development of melasma.[14] Lipid peroxidation in cell membranes is one of the main pathways of tissue damage caused by oxidative stress, and malondialdehyde (MDA) is the end product of this mechanism.

Serum MDA levels are also high in melasma patients, while serum catalase levels are decreased.[6,15] This is supported by the research of Rahimi, et al. who reported significantly higher serum MDA levels in subjects with melasma compared to non-melasma subjects (3.08 vs 2.35/ml; p <0.05) and this is positively-correlated with melasma severity (r=0.4, p<0.001). Serum MDA concentration is an indicator of oxidative stress damage in melasma.[16]

Seckin, et al. have proven the influence of oxidative stress in melasma and reported significant increases in serum superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) levels in melasma patients compared to control subjects.[17] Moreover, another study by Choubey, et al. involving 50 melasma patients and 50 non-melasma patients as controls showed that serum levels of MDA, SOD, and GSH-Px, which are the main antioxidant enzymes, were significantly increased in melasma patients compared to non-melasma subjects.[18,19] This illustrates that oxidative stress plays a role in the pathogenesis of melasma; thus, antioxidants such as melatonin can inhibit oxidative damage caused by free radicals.[20,21]

Melatonin and its metabolites, namely N-acetyl-5-Methoxykynuramine and cyclic-30 hydroxymelatonin, plays a significant role in preventing ROS and reactive nitrogen species (RNS) and in protecting melanocytes from oxidative damage.[18,20,22] This protective function is strengthened by melatonin binding to the MT 1/2 receptor, which stimulates the expression of some antioxidant enzymes such as SOD 1,2, glutathione peroxidase, and GSH reductase.[18,23] Melatonin is a potent indirect antioxidant that can scavenge free radicals and stabilize cell membranes, leading to better resistance against oxidative damage. Melatonin can inhibit the synthesis of inducible nitric oxide synthase (iNOS) induced by UV radiation. The synthesis of iNOS affects the metabolism of α-MSH, estrogen, and progesterone in melasma.[24] Sarkar, et al. reported that serum levels of melatonin and catalase were decreased in melasma patients compared to non-melasma patients, while serum levels of protein carbonyl and nitric oxide (NO) were increased.[6]

In the present study, the median melatonin level in melasma subjects is lower than in controls (92.480 ng/L vs. 436.355 ng/L; p<0.001). Melatonin and its metabolites directly affect melanogenesis by inhibiting tyrosinase activity and melanocyte proliferation. Melatonin inhibits melanogenesis not only through stimulation of MT1/2 receptors but also indirectly through estrogen desensitization, reduction of skin sensitivity to α-MSH stimulation,[25] and activation of nuclear factor erythroid 2-related factor 2 (Nrf2) and phosphatidylinositol 3-kinase-protein kinase B (PI3K-PKB)/Akt pathways and signaling. Mitogen-activated protein kinase (MAPK) causes a decrease in transcription of tyrosinase related protein (TRP)-1 and TRP-2, resulting in a decrease in melanogenesis.[11,26]

The melatonin mechanism regulates physiological melanogenesis through calcium calmodulin

complex, iNOS, p53, cytochrome c, electron transport chain (ETC) enzyme, SIRT3/SOD2, and NQO2 (N-ribosyldihydronicotinamide: Quinone reductase 2). Melatonin influences the transcription of the peripheral clock genes basic helix-loop-helic ARNT like 1 (BMAL-1) and decreases the melanogenesis process (e.g., decreased expression of TRP-1 and TRP-2 tyrosinase enzymes). It also decreases melanocyte activity or inhibits the proliferation of epidermal melanocytes.[11,27] The results of this study revealed a strong negative correlation (r=-0.707; p<0.001) between melatonin levels in melasma and the severity of melasma based on the MASI score. It indicates that a decrease in plasma melatonin levels is in line with the increase in the severity of melasma. Additionally, this study proved that low plasma melatonin levels in melasma subjects can increase the prevalence ratio of melasma by 2.87 times (PR 2.87; 95% CI = 1.605-5.150; p<0.001) when compared to high plasma melatonin levels. The fact that melatonin levels correlated with the severity of melasma is likely due to the function of melatonin and its metabolites, which may protect melanocytes from UVB-induced oxidative stress, minimize melanocyte DNA damage, induce repair of DNA damage, induce the expression of antioxidative enzymes in melanocytes, and influence the hormones affecting melasma pathogenesis.[24-26,28]

Another cohort study reported that patients with acanthosis nigricans treated with 3 mg/day oral melatonin showed a reduction in their hyperpigmentation.[10] Another study reported that 36 melasma patients with topical melatonin therapy and oral melatonin for 90 days had a significant reduction in MASI score.[12,29,30] Moreover, another study also revealed that melatonin application decreased skin pigmentation and increased protection against photoaging.[7,22] Future studies need to focus on melasma therapy with melatonin and its side effects, with larger sample size and longer research duration.

Conclusion

Based on the results of the present study, plasma melatonin levels are associated with the severity of melasma, as melasma subjects have a lower plasma melatonin level compared to non-melasma subjects. Plasma melatonin levels negatively-correlate with the severity of melasma.

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None.

Author Contributions

All authors act as the guarantors of the manuscript IGAAP plays a role in developing research concepts and ideas. IGASP was responsible for data collection. NS and CK contributed to data analysis and interpretation. IGAAEI and IGAAP participated in writing the study.

Conflict of Interest

No conflict of interest.

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